

# EXHIBIT 1



US006827901B2

(12) United States Patent  
Copeland et al.

(10) Patent No.: US 6,827,901 B2  
(45) Date of Patent: Dec. 7, 2004

- (54) AUTOMATED BIOLOGICAL REACTION APPARATUS

- (56) References Cited

U.S. PATENT DOCUMENTS

- |             |         |                      |         |
|-------------|---------|----------------------|---------|
| 3,219,416 A | 11/1965 | Natelson .....       | 23/253  |
| 3,398,935 A | 8/1968  | Livesey et al. ....  | 259/18  |
| 3,482,082 A | 12/1969 | Israeli .....        |         |
| 3,574,064 A | 4/1971  | Binnings et al. .... | 195/127 |
| 3,644,715 A | 2/1972  | Holderith .....      |         |

(List continued on next page.)

- (75) Inventors: Keith G. Copeland, Tucson, AZ (US); Thomas M. Grogan, Tucson, AZ (US); Charles Hassen, Tucson, AZ (US); William Ross Humphreys, Tucson, AZ (US); Charles D. Lemme, Tucson, AZ (US); Phillip C. Miller, Tucson, AZ (US); William L. Richards, Tucson, AZ (US); Wayne A. Showalter, Tucson, AZ (US)

- (73) Assignee: Ventana Medical Systems, Inc.  
Tucson, AZ (US)

- EP 0 285 851 10/1988  
EP 0290018 11/1988

(List continued on next page.)

- (\*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

- (21) Appl. No.: 10/137,169

- (22) Filed: May 2, 2002

#### OTHER PUBLICATIONS

- E. Stark et al., "An automated device for immunocytochemistry," Journal of Immunological Methods 107:89-92 (1988).

(List continued on next page.)

#### Related U.S. Application Data

- (63) Continuation of application No. 09/931,513, filed on Aug. 16, 2001, which is a continuation of application No. 09/452,309, filed on Dec. 1, 1999, now Pat. No. 6,352,861, which is a continuation of application No. 08/906,678, filed on Aug. 5, 1997, now abandoned, which is a continuation of application No. 08/479,415, filed on Jun. 6, 1995, now Pat. No. 5,654,200, which is a division of application No. 08/352,966, filed on Dec. 9, 1994, now Pat. No. 5,595,707, which is a continuation of application No. 07/924,052, filed on Aug. 31, 1992, now abandoned, which is a continuation-in-part of application No. 07/488,601, filed on Mar. 2, 1990, now abandoned.

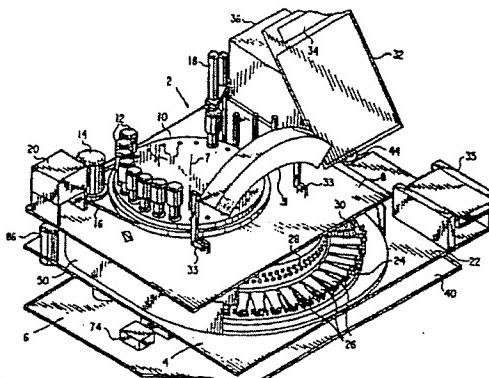
- (51) Int. Cl.<sup>7</sup> ..... G01N 35/00  
(52) U.S. Cl. ..... 422/64; 422/62; 422/67;  
436/43; 436/45; 436/46; 436/54; 436/55

- (58) Field of Search ..... 436/43, 45, 46,  
436/48, 49, 54-55; 422/62, 64, 67

## ABSTRACT

An automated immunostaining apparatus having a reagent application zone and a reagent supply zone. The apparatus has a carousel slide support supporting a plurality of slide supports thereon, and drive means engaging the carousel slide support for consecutively positioning each of a plurality of slide supports in the reagent application zone. The apparatus also has a carousel reagent support having a plurality of reagent container supports thereon, and drive means engaging the carousel for rotating the carousel and positioning a preselected reagent container support in the reagent supply zone. The apparatus also has a reagent delivery actuator means positioned for engaging a reagent container positioned on a container support.

45 Claims, 37 Drawing Sheets



## US 6,827,901 B2

Page 2

## U.S. PATENT DOCUMENTS

3,660,638 A	5/1972	Oberli	5,031,797 A	7/1991	Boris et al.
3,772,154 A	11/1973	Isenberg et al.	5,051,238 A	9/1991	Umetsu et al.
3,831,006 A	8/1974	Chaffin, III et al.	5,059,393 A	10/1991	Quenin et al.
3,853,092 A	12/1974	Amos et al. ....	5,073,504 A	12/1991	Bogen
3,854,703 A	12/1974	Gibbs et al. ....	5,075,079 A	12/1991	Kerr et al.
3,909,203 A	9/1975	Young et al.	5,081,038 A	1/1992	Sugaya et al.
3,916,157 A	10/1975	Roulette et al.	5,102,624 A	4/1992	Muraishi
4,013,038 A	3/1977	Rogers et al. ....	5,106,583 A	4/1992	Raysberg et al.
4,066,412 A	1/1978	Johnson et al.	5,107,422 A	4/1992	Kamenitsky et al. ....
4,092,952 A	6/1978	Wilkie et al. ....	5,122,342 A	6/1992	McCulloch et al.
4,113,437 A	9/1978	Duff et al.	5,180,606 A	1/1993	Stokes et al.
4,133,642 A	1/1979	Nosaka et al.	5,229,074 A	7/1993	Heath et al.
4,135,883 A	1/1979	McNeil et al.	5,232,664 A	8/1993	Krawzak et al.
4,159,875 A	7/1979	Hauser	5,250,262 A	10/1993	Heidt et al.
4,163,643 A	8/1979	Hunter et al.	5,311,426 A	5/1994	Donohue et al.
4,200,056 A	4/1980	Johnson ....	5,316,452 A	5/1994	Bogen et al.
4,200,607 A	4/1980	Suzuki	5,316,728 A	5/1994	Hayashi et al.
4,245,967 A	1/1981	Busselet	5,350,697 A	9/1994	Swope et al.
4,281,387 A	7/1981	Kraft et al.	5,355,695 A	10/1994	Kawaguchi et al.
RE30,730 E	9/1981	Duff	5,418,138 A	5/1995	Miller et al.
4,298,571 A	11/1981	DiFulvio et al. ....	5,424,036 A	6/1995	Ushikubo
4,338,279 A	7/1982	Orimo et al.	5,425,918 A	6/1995	Healey et al.
4,346,056 A	8/1982	Sakurada	5,439,645 A	8/1995	Saralegui et al.
4,371,498 A	2/1983	Scordato et al.	5,439,649 A	8/1995	Tsueung et al.
4,406,547 A	9/1983	Aihara	5,645,114 A	7/1997	Bogen et al.
4,447,395 A	5/1984	Englar et al. ....	5,646,046 A	7/1997	Fischer et al.
4,455,280 A	6/1984	Shinohara et al. ....	5,654,200 A	8/1997	Copeland et al.
4,517,160 A	5/1985	Galle et al.	5,656,493 A	8/1997	Mullis et al.
4,528,159 A	7/1985	Liston	5,947,167 A	9/1999	Bogen et al.
4,558,946 A	12/1985	Galle et al.	6,193,933 B1	2/2001	Sasaki et al.
4,567,748 A	2/1986	Klass et al.			
4,585,622 A	4/1986	Bowe et al.	FR	2239167	7/1973
4,634,576 A	1/1987	Galle et al.	FR	2258122	6/1982
4,643,879 A	2/1987	Hanaway	GB	2216259	10/1989
4,647,432 A	3/1987	Wakatake	JP	55107957	8/1980
4,656,006 A	4/1987	Assmann et al.	JP	61076122	10/1987
4,664,526 A	5/1987	Scheffler et al. ....	JP	6114064	1/1988
4,675,299 A	6/1987	Witty et al.	JP	61190061	2/1988
4,678,752 A	7/1987	Thorne et al.	JP	61205089	3/1988
4,678,894 A	7/1987	Shafer	JP	61242989	4/1988
4,681,741 A	7/1987	Hanaway	JP	61275282	6/1988
4,683,120 A	7/1987	Meserol et al.	JP	62202748	2/1989
4,692,308 A	9/1987	Riley et al.	JP	63082232	10/1989
4,708,886 A	11/1987	Nelson	JP	63144871	12/1999
4,719,087 A	1/1988	Hanaway	WO	8503571	8/1985
4,727,033 A	2/1988	Hijikata et al.	WO	8700086	1/1987
4,729,661 A	3/1988	Bell	WO	8802865	4/1988
4,764,342 A	8/1988	Kelln et al. ....	WO	WO 88/02866	4/1988
4,774,055 A	9/1988	Wakatake et al. ....	WO	WO 89/01616	2/1989
4,781,891 A	11/1988	Galle et al. ....			
4,795,613 A	1/1989	Azuma et al.			
4,795,710 A	1/1989	Muszak et al. ....	FR	2239167	7/1973
4,808,380 A	2/1989	Minekane	FR	2258122	6/1982
4,815,978 A	3/1989	Mazza et al. ....	GB	2216259	10/1989
4,824,641 A	4/1989	Williams	JP	55107957	8/1980
4,844,868 A	7/1989	Rokugawa	JP	61076122	10/1987
4,844,887 A	7/1989	Galle et al.	JP	6114064	1/1988
4,847,208 A	7/1989	Bogen	JP	61190061	2/1988
4,849,177 A	7/1989	Jordan	JP	61205089	3/1988
4,855,109 A	8/1989	Muraishi et al.	JP	61242989	4/1988
4,855,110 A	8/1989	Marker et al.	JP	61275282	6/1988
4,865,811 A	9/1989	Newton et al.	JP	62202748	2/1989
4,900,513 A	2/1990	Barker et al.	JP	63082232	10/1989
4,919,887 A	4/1990	Wakatake	JP	63144871	12/1999
4,933,147 A	6/1990	Hollar et al.	WO	8503571	8/1985
4,935,875 A	6/1990	Shah et al.	WO	8700086	1/1987
4,943,415 A	7/1990	Przybylowicz et al.	WO	8802865	4/1988
4,961,906 A	10/1990	Andersen et al.	WO	WO 88/02866	4/1988
4,965,049 A	10/1990	Lillig et al. ....	WO	WO 89/01616	2/1989
4,985,206 A	1/1991	Bowman et al.			
4,988,482 A	1/1991	Weston			

## FOREIGN PATENT DOCUMENTS

FR	2239167	7/1973
FR	2258122	6/1982
GB	2216259	10/1989
JP	55107957	8/1980
JP	61076122	10/1987
JP	6114064	1/1988
JP	61190061	2/1988
JP	61205089	3/1988
JP	61242989	4/1988
JP	61275282	6/1988
JP	62202748	2/1989
JP	63082232	10/1989
JP	63144871	12/1999
WO	8503571	8/1985
WO	8700086	1/1987
WO	8802865	4/1988
WO	WO 88/02866	4/1988
WO	WO 89/01616	2/1989

## OTHER PUBLICATIONS

- Saiki et al., "Enzymatic Amplification of  $\beta$ -Globin Genomic Sequences and Restriction Site Analysis for Diagnosis of Sickle Cell Anemia," *Science*, 230:1350-1353, Dec. 20, 1985.
- Innis et al., "DNA sequencing with *Thermus aquaticus* DNA polymerase and direct sequencing of polymerase chain reaction-amplified DNA," *Proc. Natl. Acad. Sci. USA*, 85:9436-9440, Dec. 1988.
- Lindeman et al., "Evaluation of the automation of immunoenzymatic procedures in a routine histo/cytopathological laboratory," *Histopathology*, 6:739-746, 1982.
- Catalog, "Fisher 86," Allied Fisher Scientific, pp. 93-99.
- Driscoll et al., "Discrete Automated Chemistry System with Tableted Reagents", *Clin. Chem.*, 29/9, pp. 1609-1615 (1983).

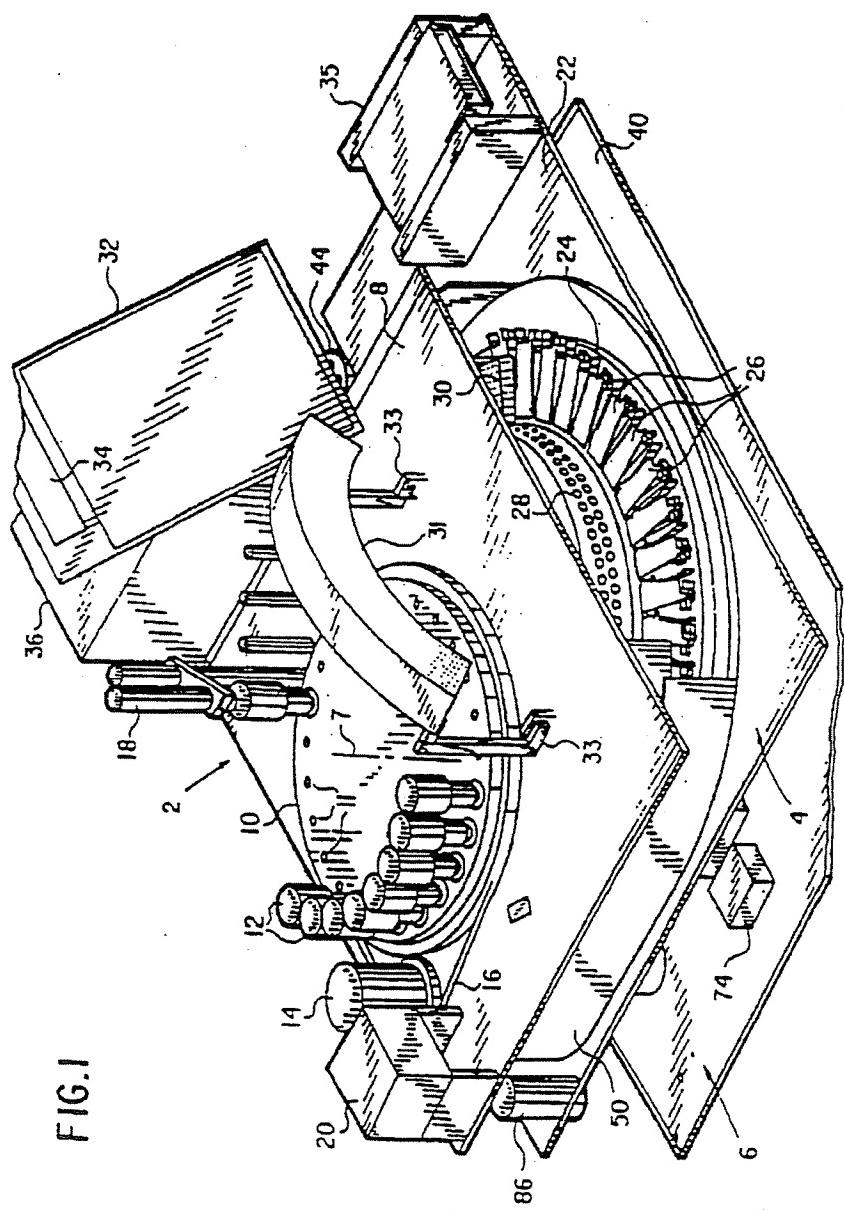
\* cited by examiner

U.S. Patent

Dec. 7, 2004

Sheet 1 of 37

US 6,827,901 B2

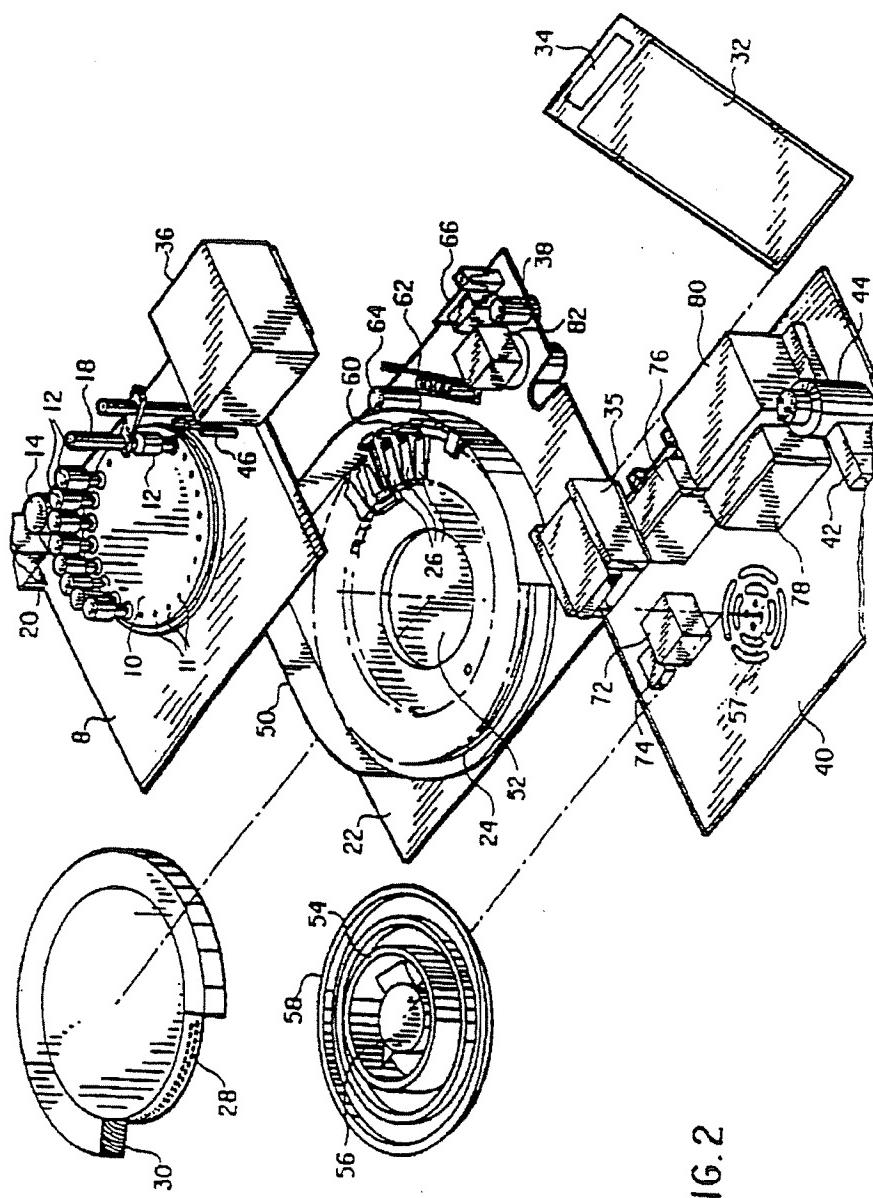


U.S. Patent

Dec. 7, 2004

Sheet 2 of 37

US 6,827,901 B2



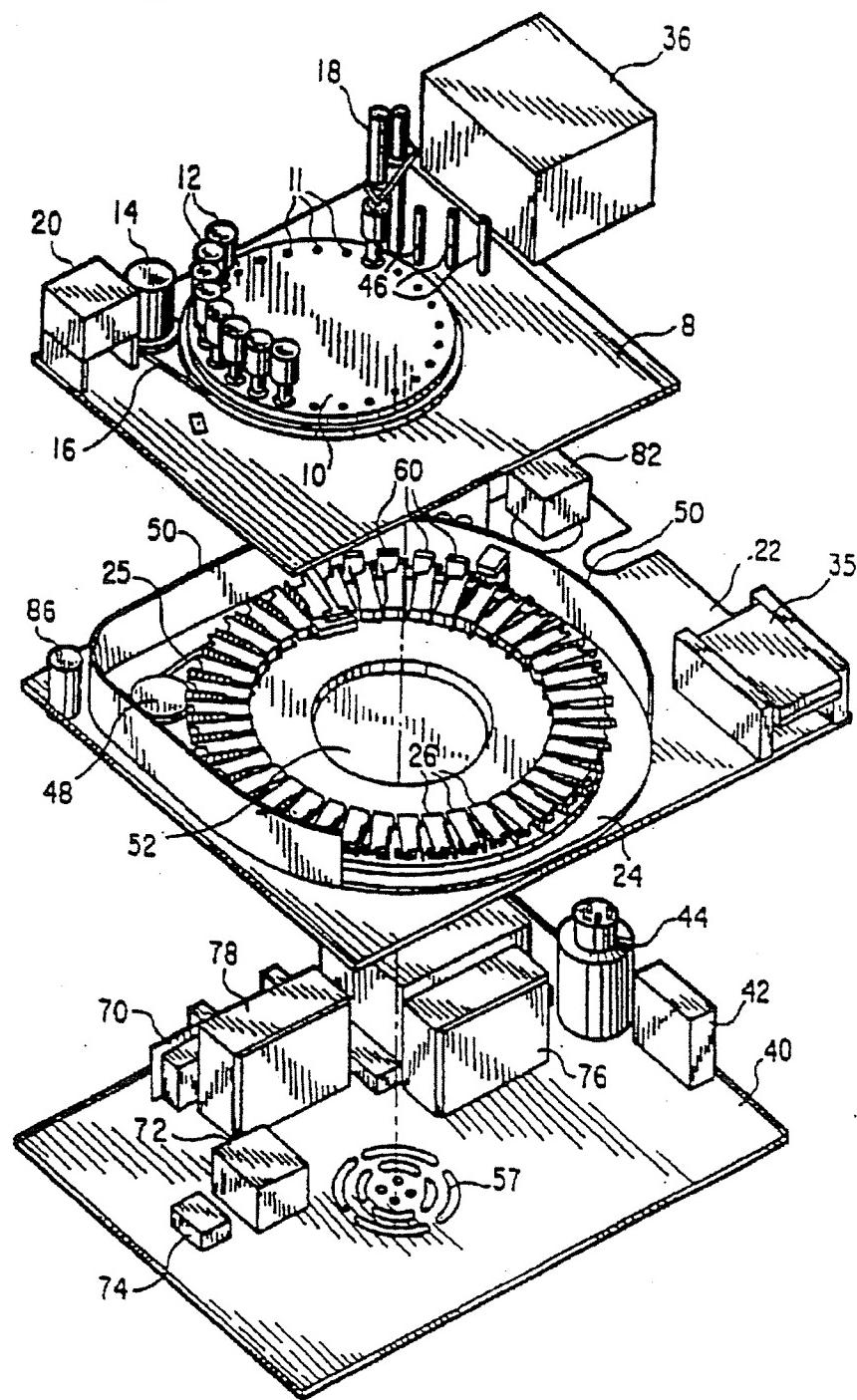
U.S. Patent

Dec. 7, 2004

Sheet 3 of 37

US 6,827,901 B2

FIG.3



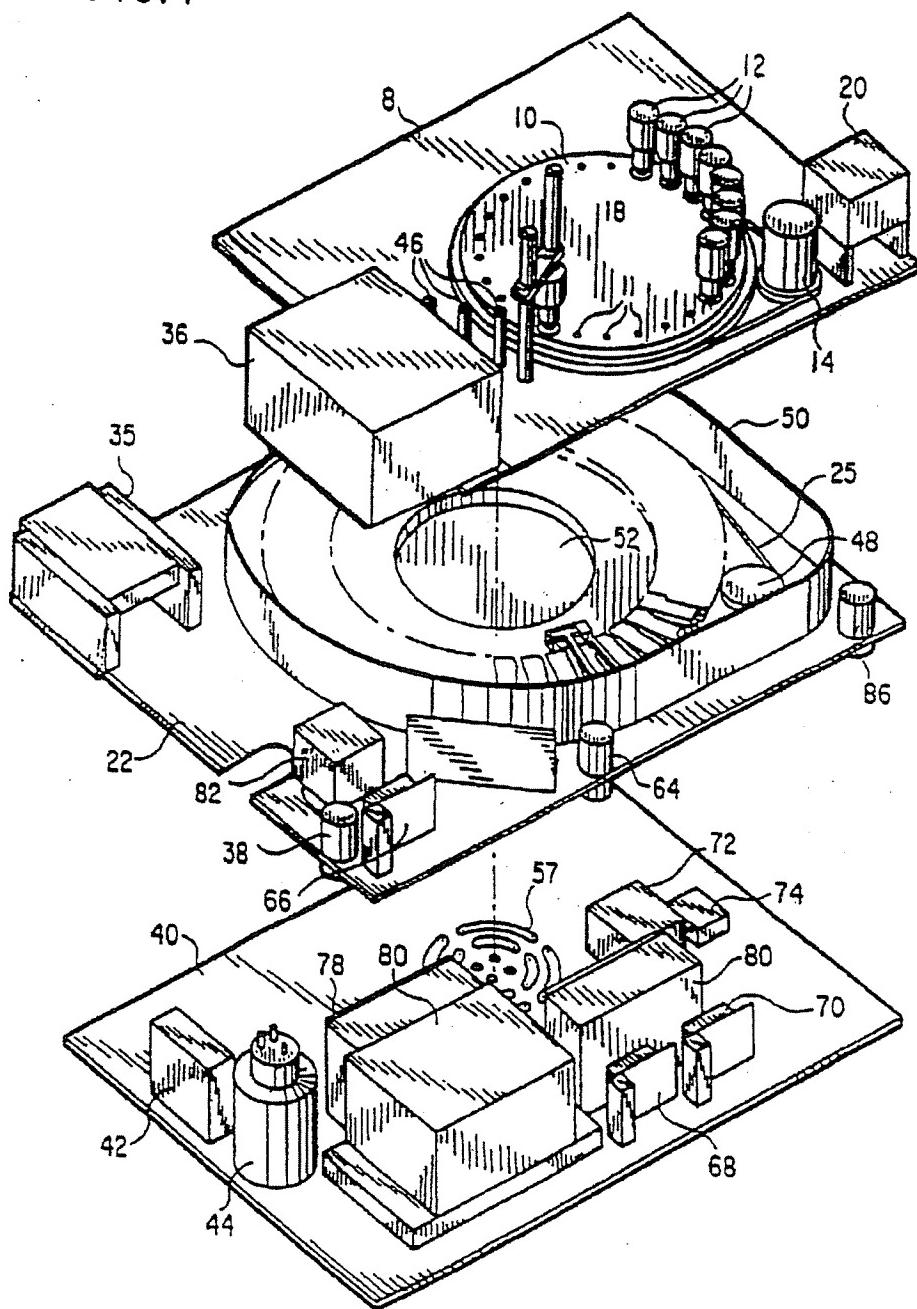
U.S. Patent

Dec. 7, 2004

Sheet 4 of 37

US 6,827,901 B2

FIG. 4



U.S. Patent

Dec. 7, 2004

Sheet 5 of 37

US 6,827,901 B2

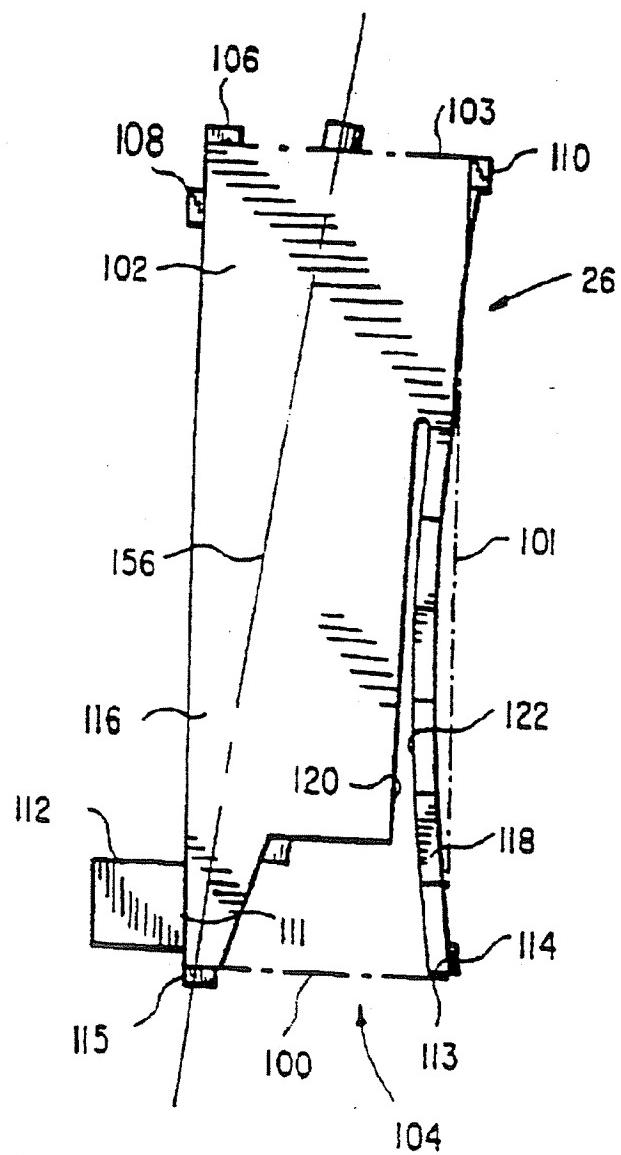


FIG. 5

U.S. Patent

Dec. 7, 2004

Sheet 6 of 37

US 6,827,901 B2

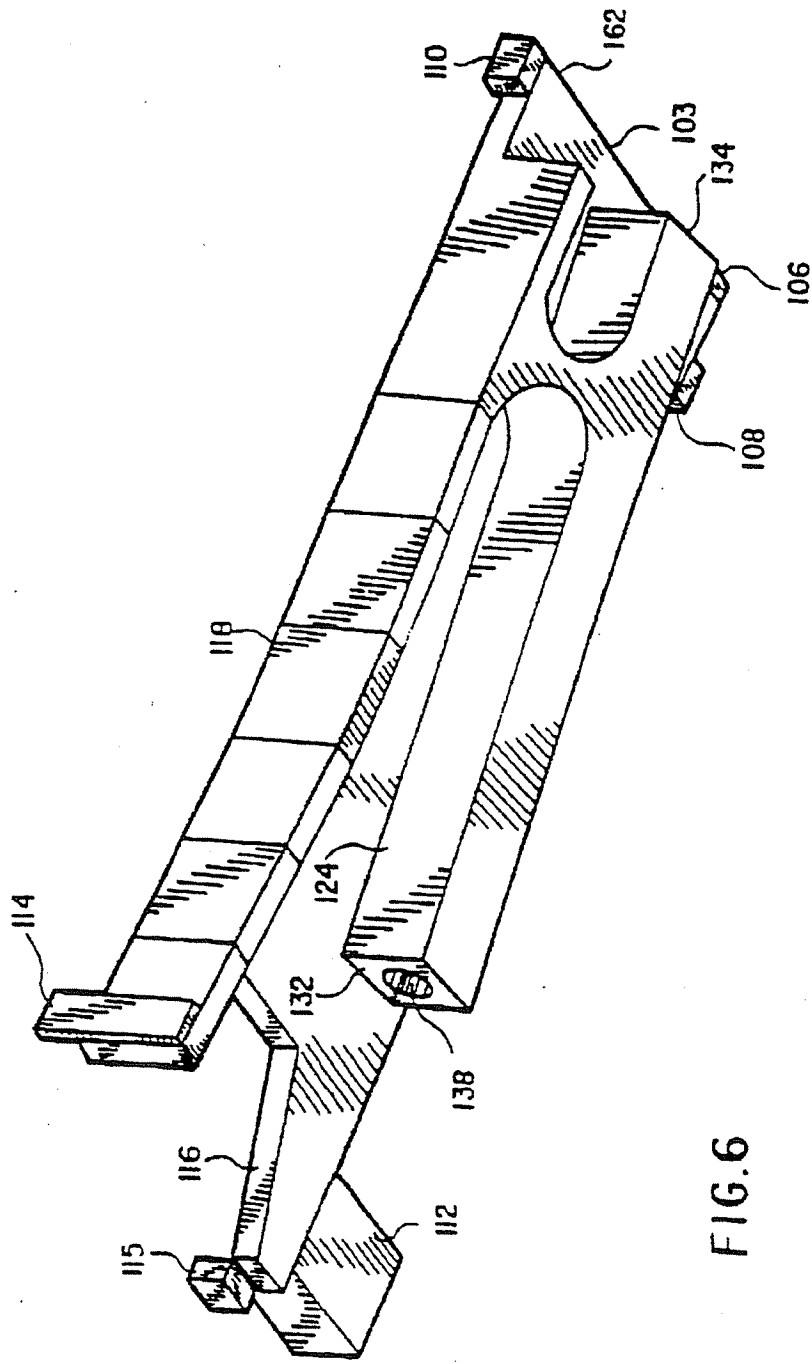


FIG. 6

U.S. Patent

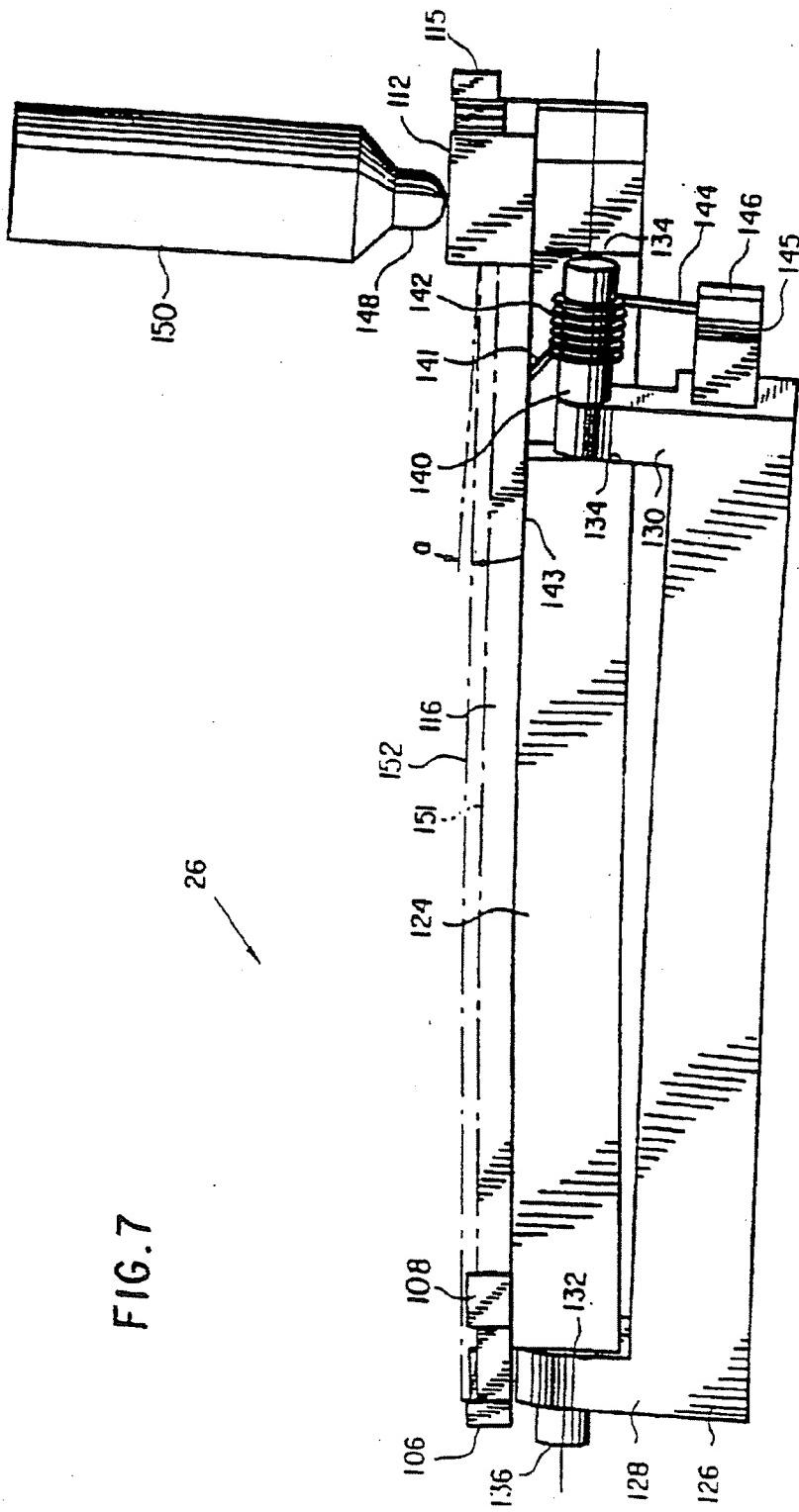
Dec. 7, 2004

Sheet 7 of 37

US 6,827,901 B2

FIG. 7

26

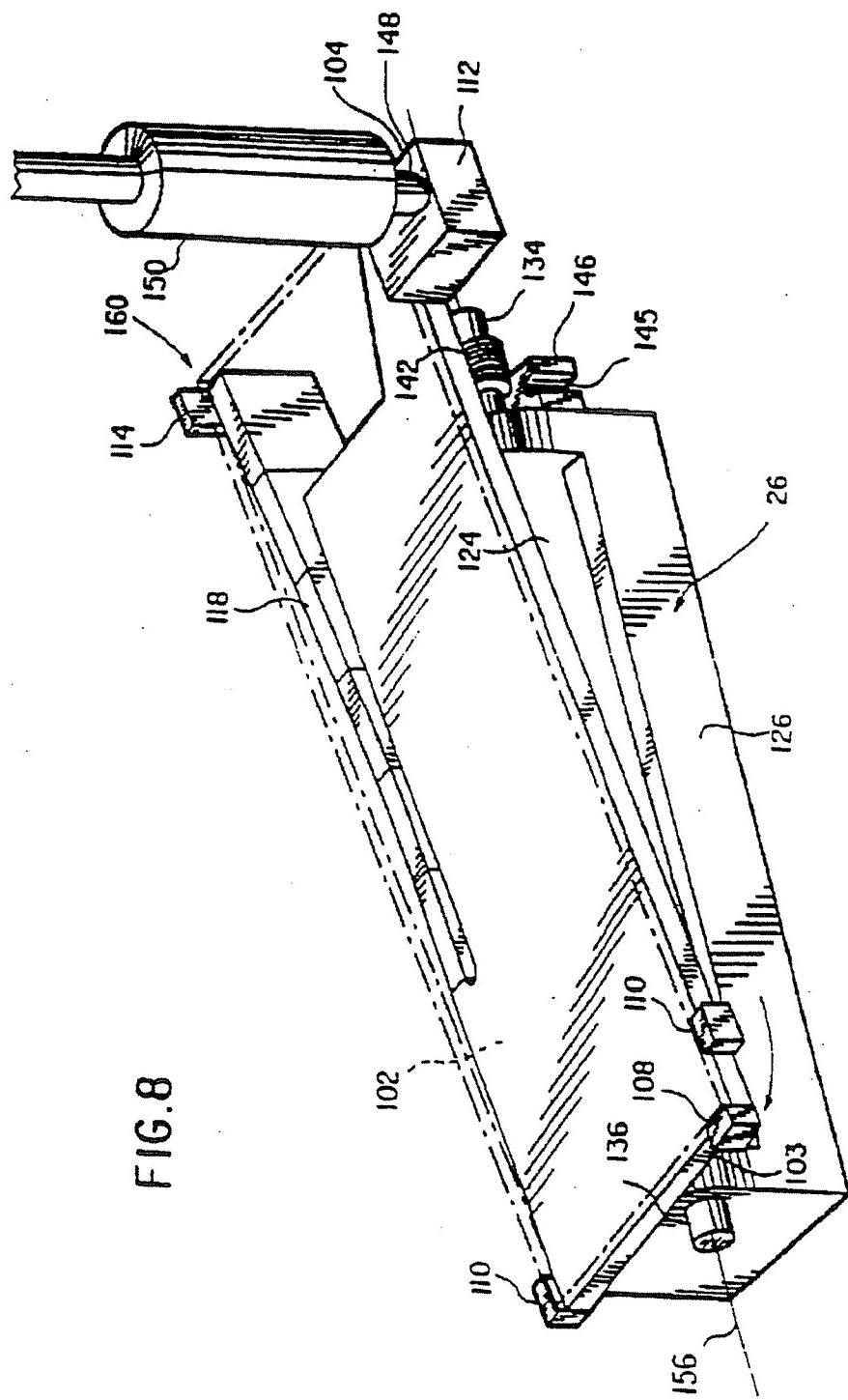


U.S. Patent

Dec. 7, 2004

Sheet 8 of 37

US 6,827,901 B2

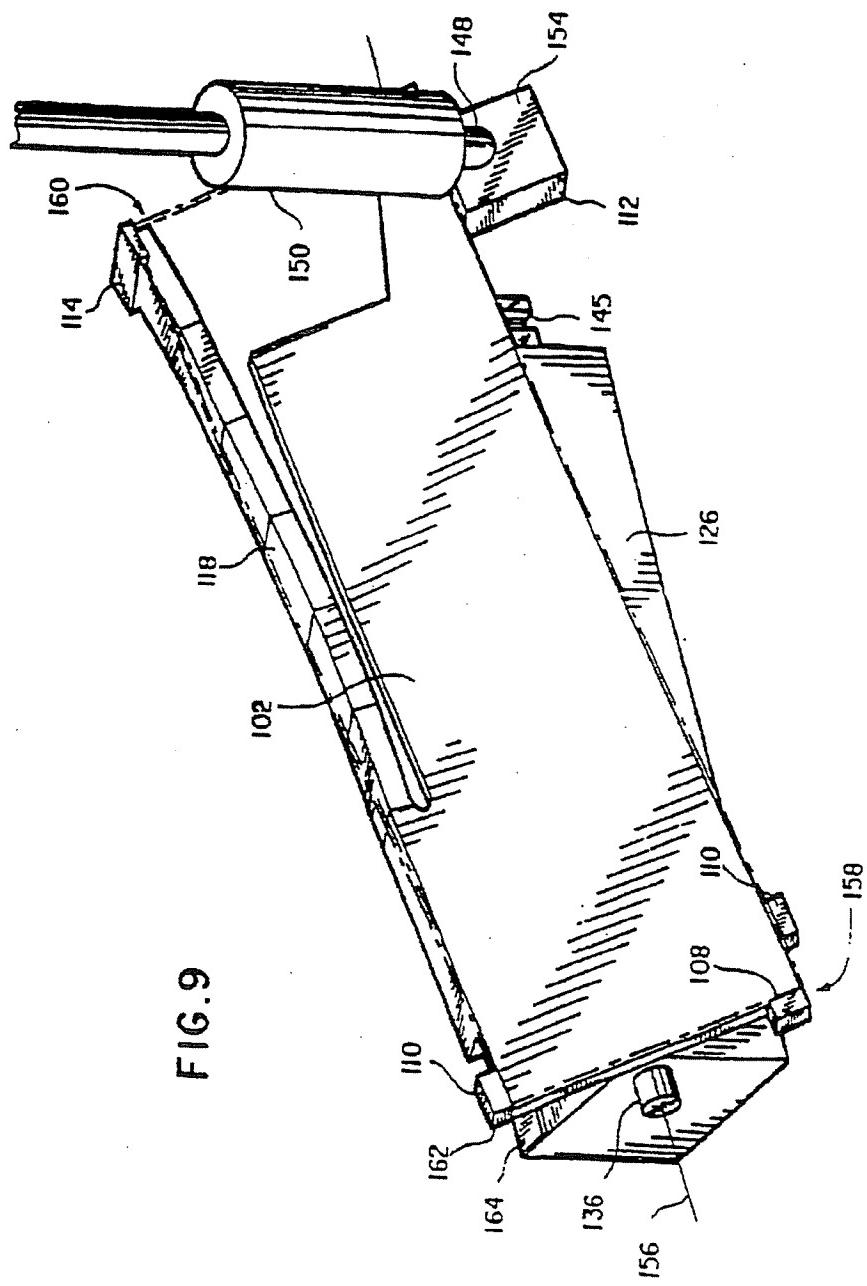


U.S. Patent

Dec. 7, 2004

Sheet 9 of 37

US 6,827,901 B2



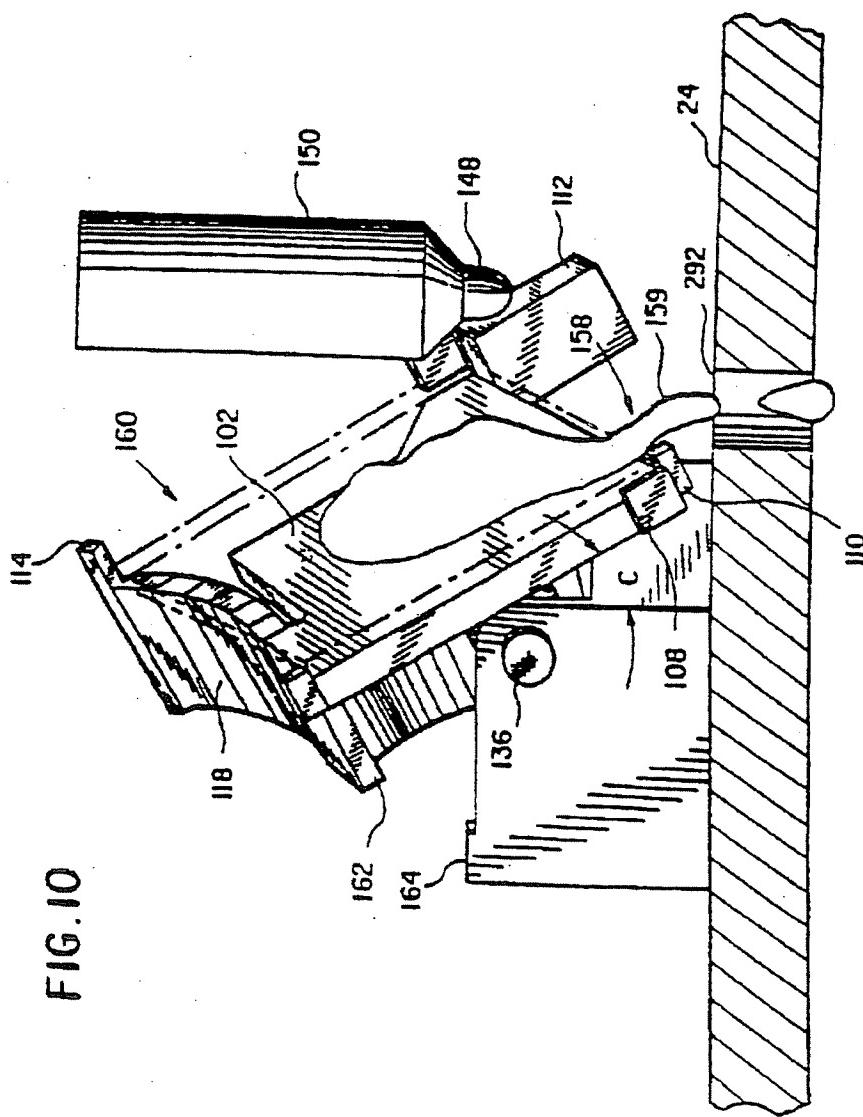
6.  
E

U.S. Patent

Dec. 7, 2004

Sheet 10 of 37

US 6,827,901 B2

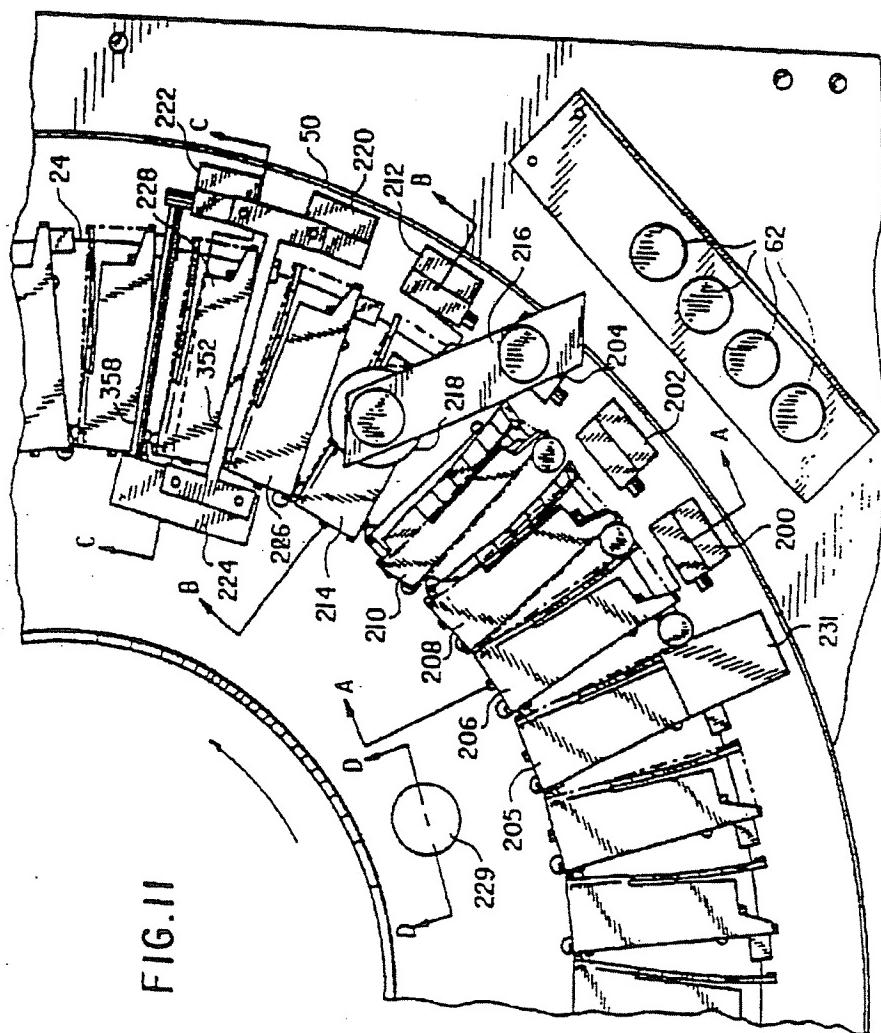


U.S. Patent

Dec. 7, 2004

Sheet 11 of 37

US 6,827,901 B2



U.S. Patent

Dec. 7, 2004

Sheet 12 of 37

US 6,827,901 B2

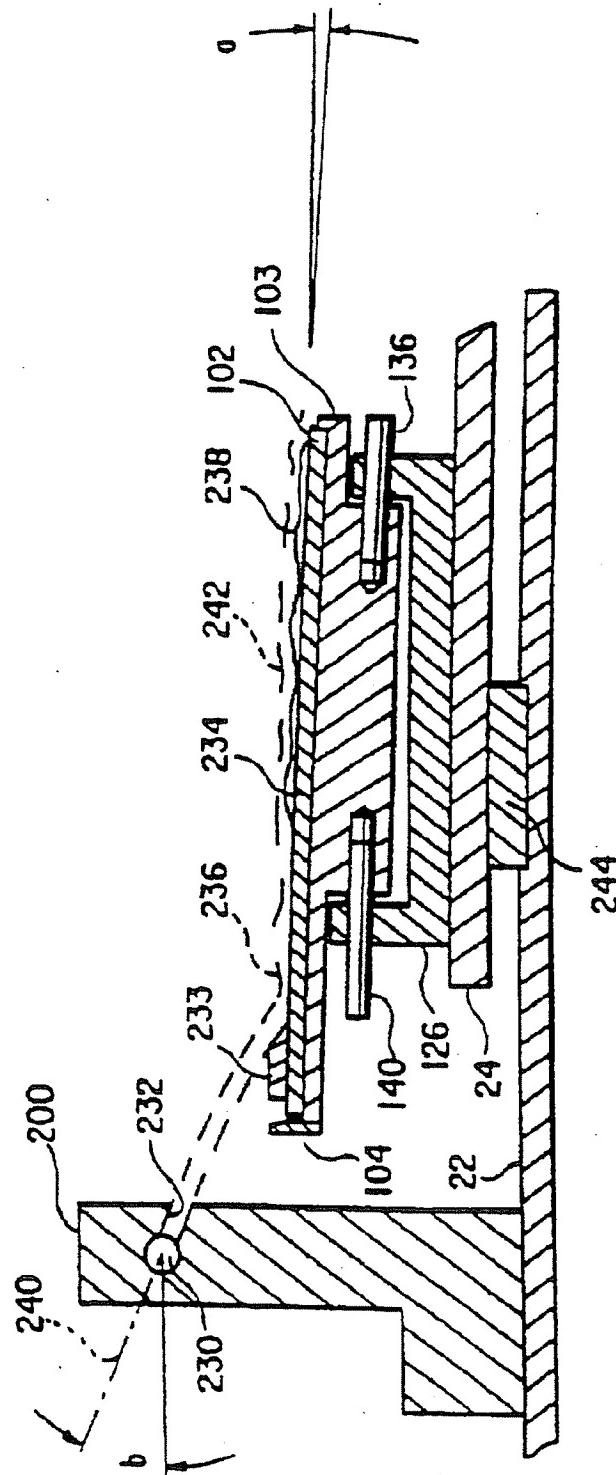


FIG. 12

U.S. Patent

Dec. 7, 2004

Sheet 13 of 37

US 6,827,901 B2

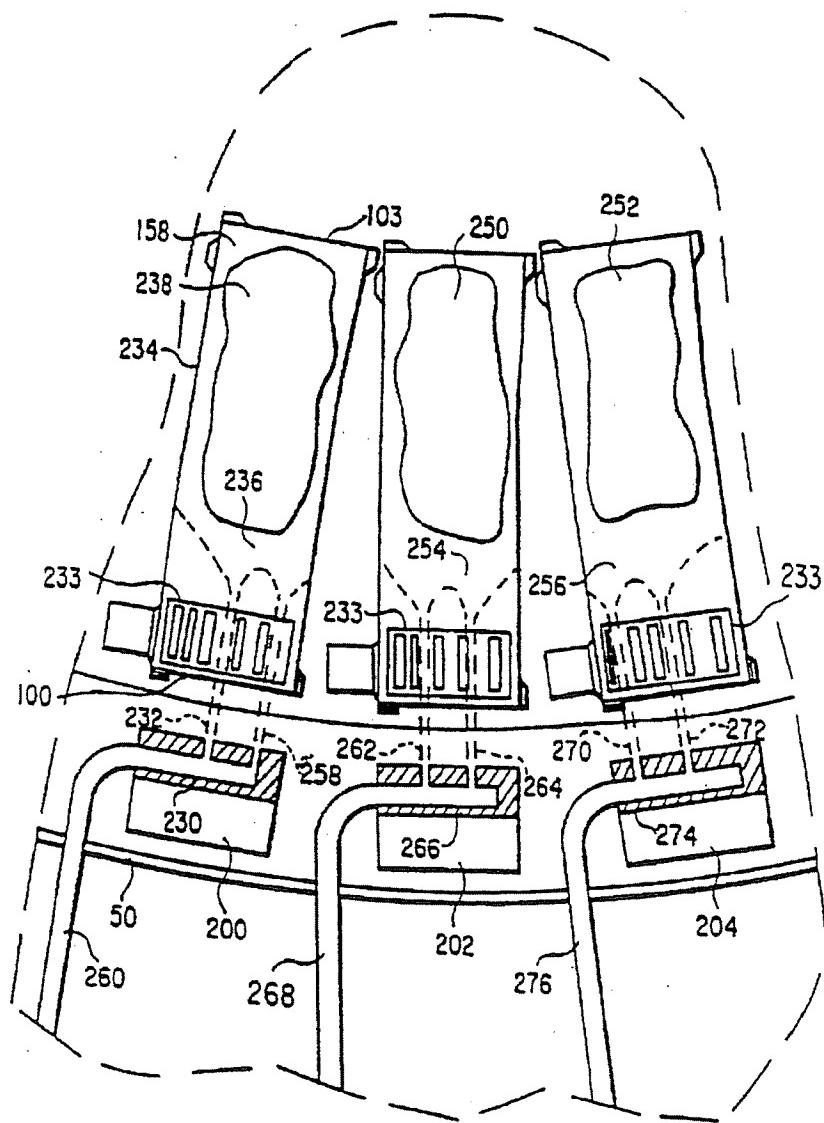


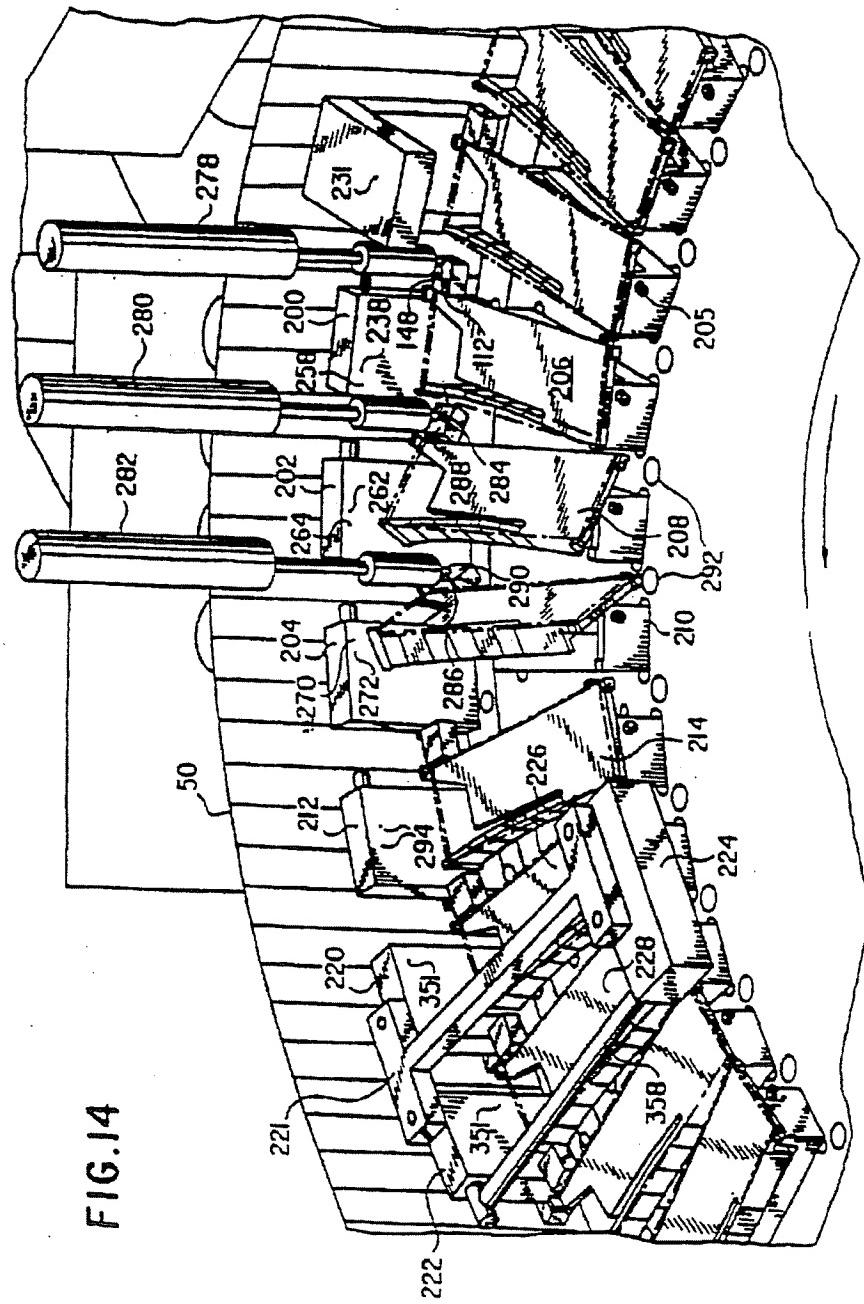
FIG.13

U.S. Patent

Dec. 7, 2004

Sheet 14 of 37

US 6,827,901 B2

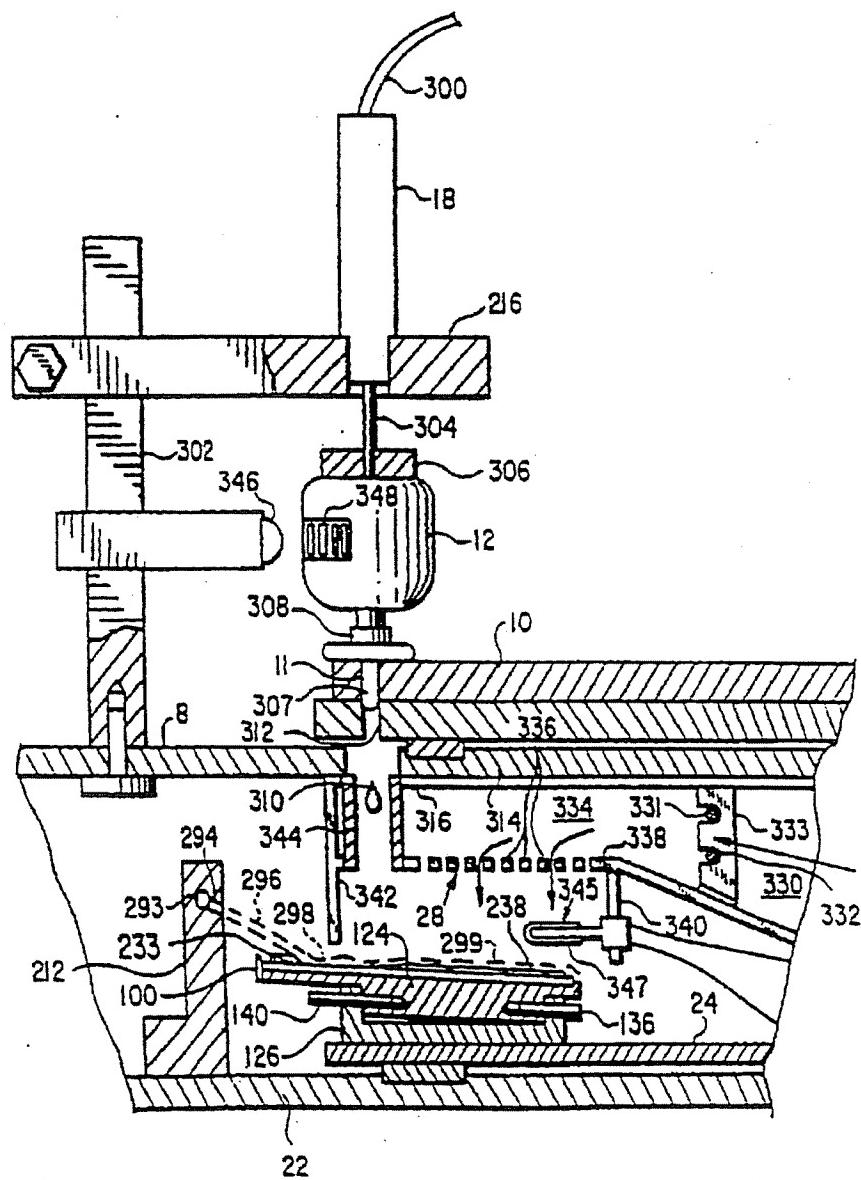


U.S. Patent

Dec. 7, 2004

Sheet 15 of 37

US 6,827,901 B2

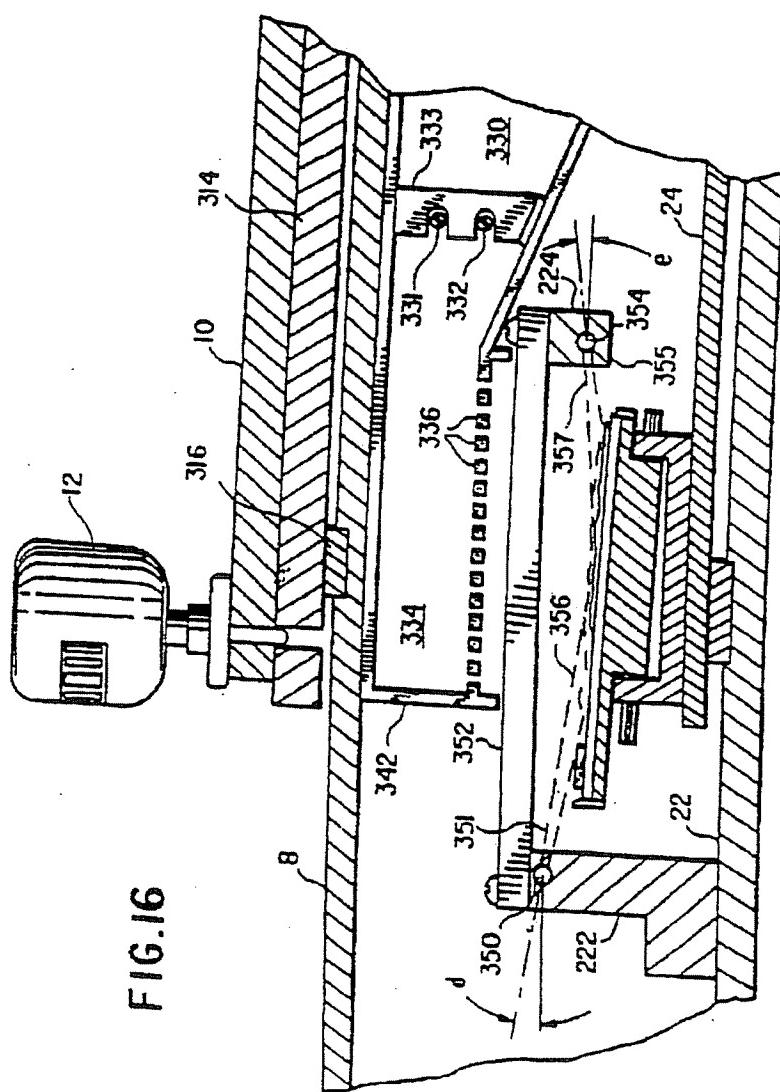


U.S. Patent

Dec. 7, 2004

Sheet 16 of 37

US 6,827,901 B2

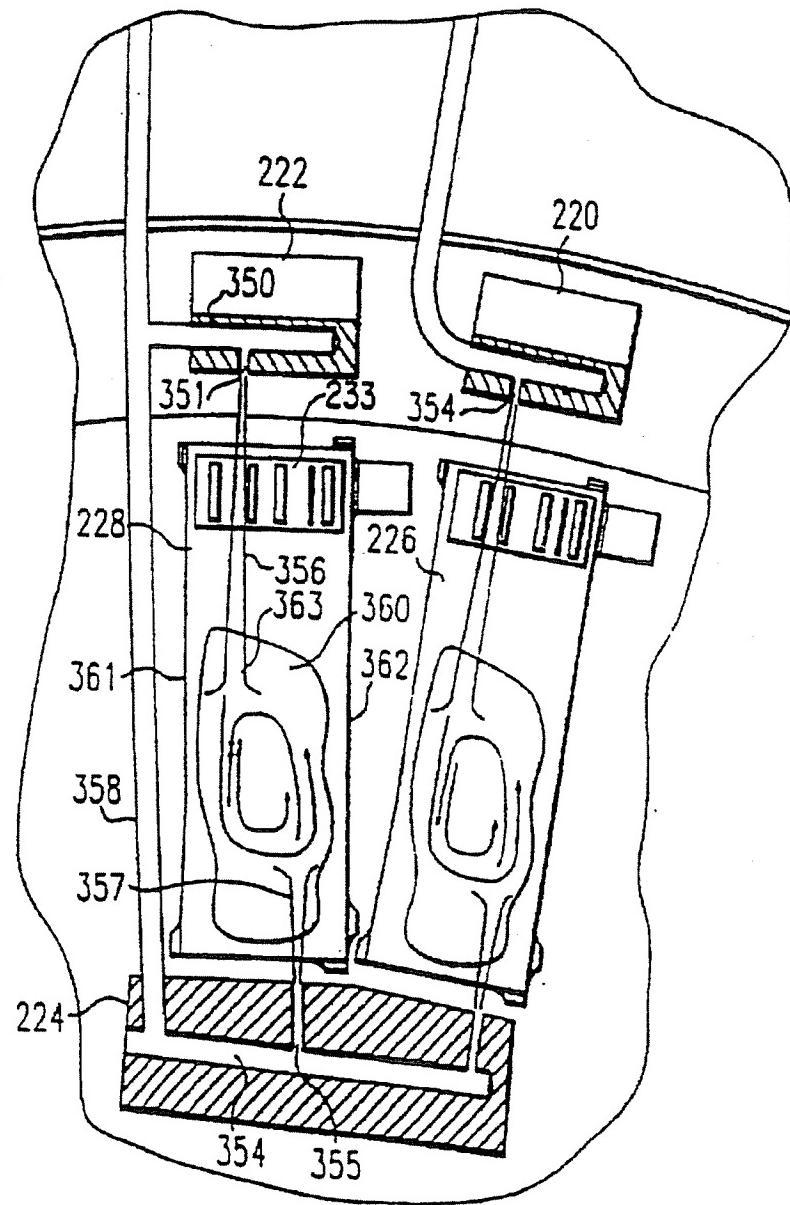


U.S. Patent

Dec. 7, 2004

Sheet 17 of 37

US 6,827,901 B2



*FIG. 17*

U.S. Patent

Dec. 7, 2004

Sheet 18 of 37

US 6,827,901 B2

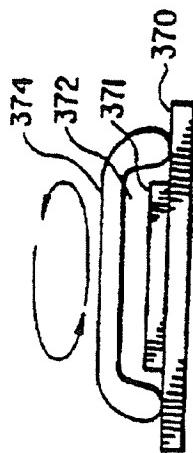


FIG. 18C

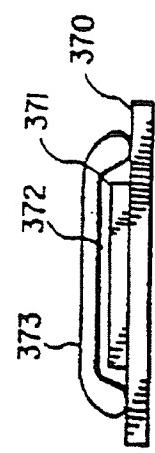


FIG. 18B

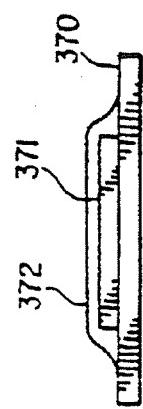


FIG. 18A

U.S. Patent

Dec. 7, 2004

Sheet 19 of 37

US 6,827,901 B2

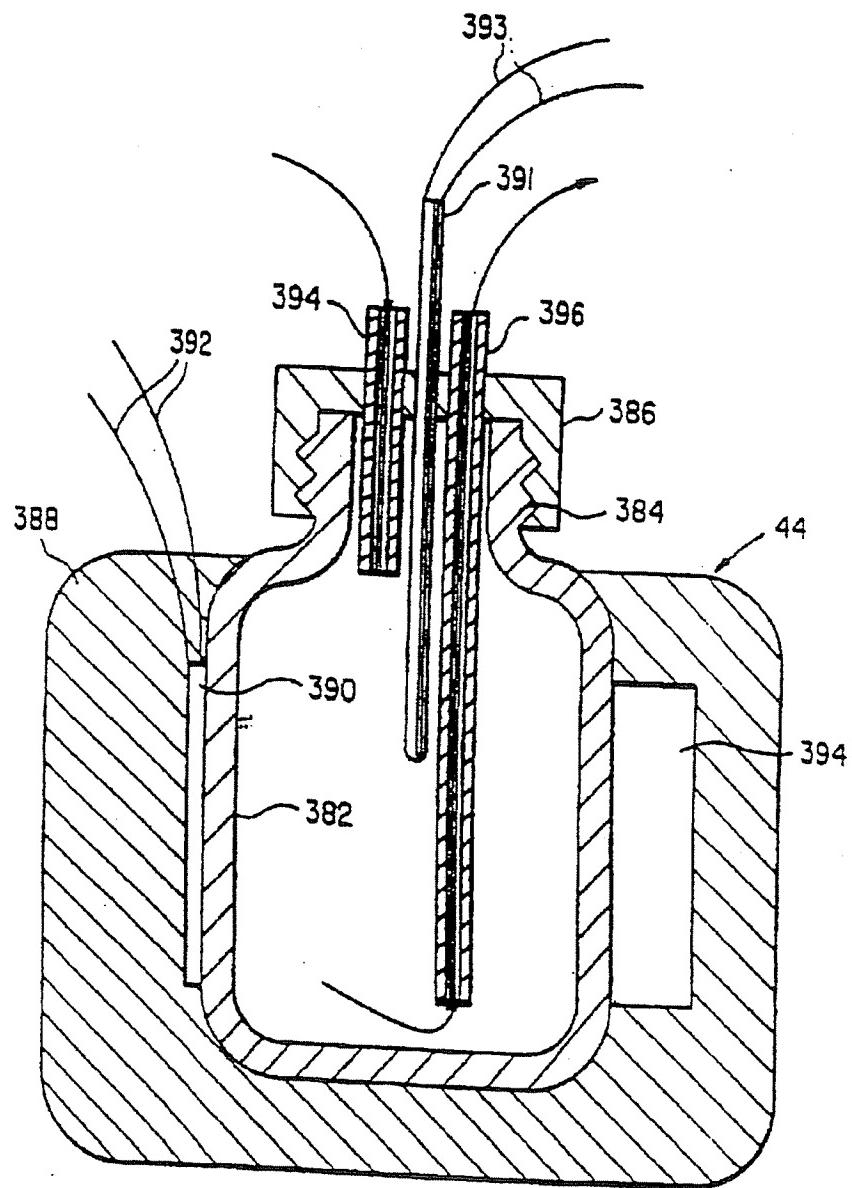


FIG. 19A

U.S. Patent

Dec. 7, 2004

Sheet 20 of 37

US 6,827,901 B2

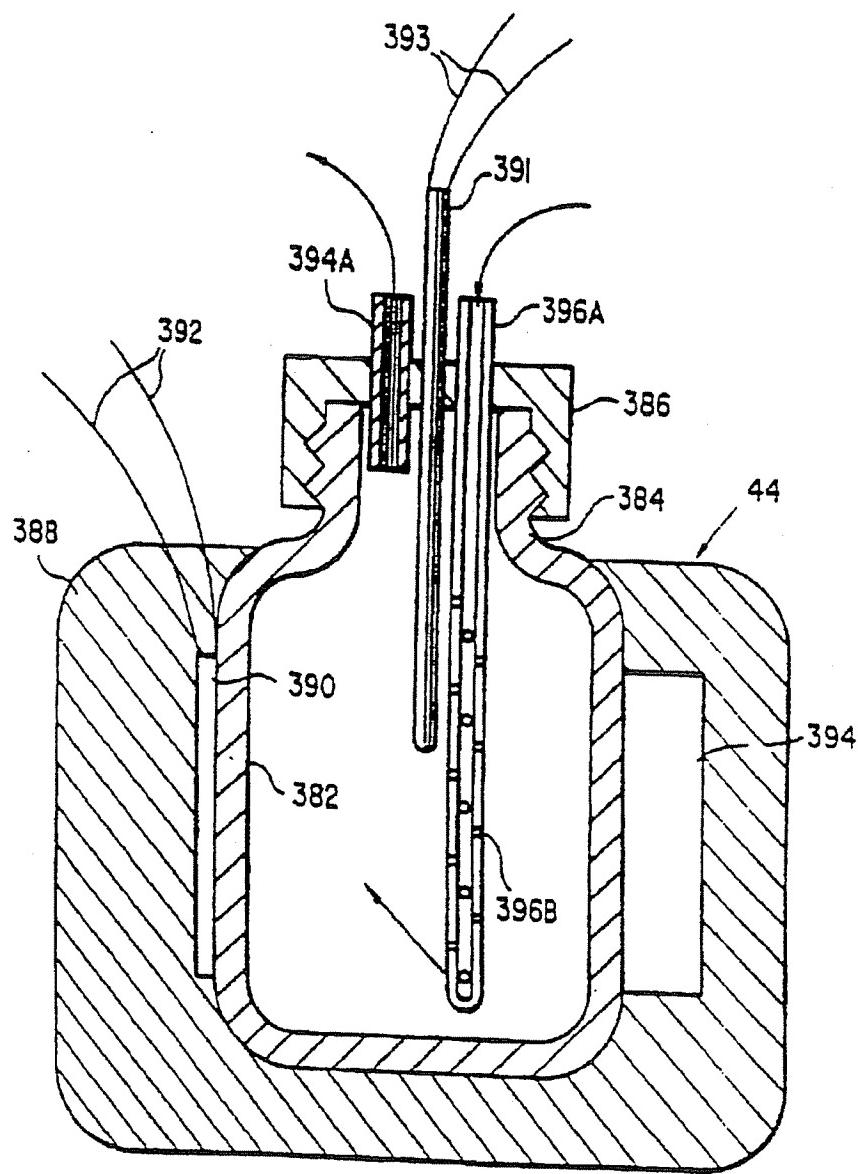


FIG. 19B

U.S. Patent

Dec. 7, 2004

Sheet 21 of 37

US 6,827,901 B2

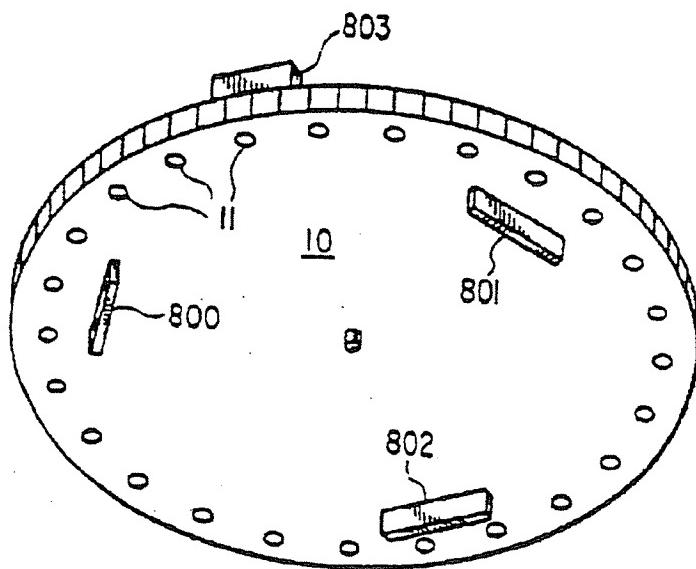


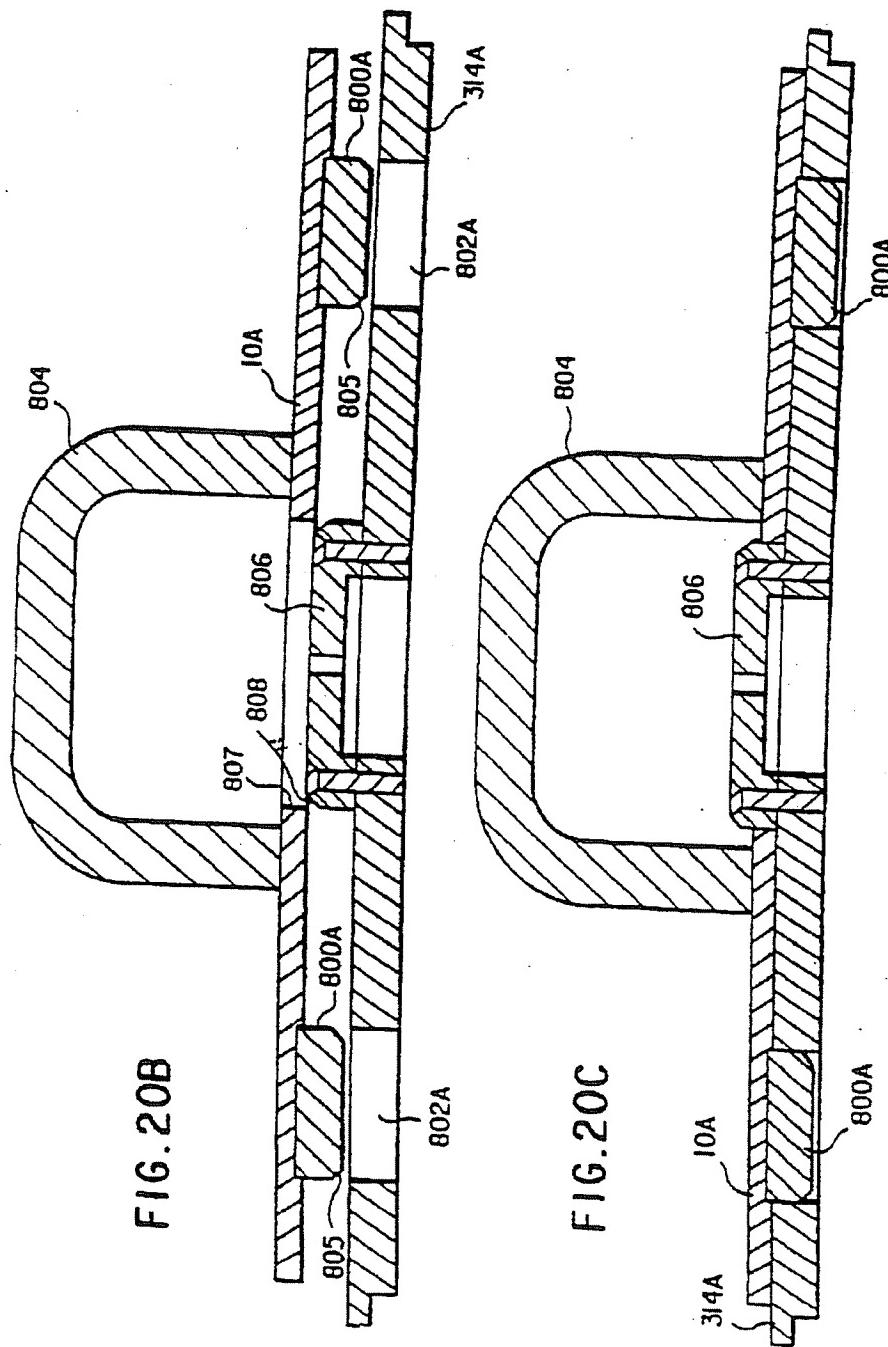
FIG.20A

U.S. Patent

Dec. 7, 2004

Sheet 22 of 37

US 6,827,901 B2



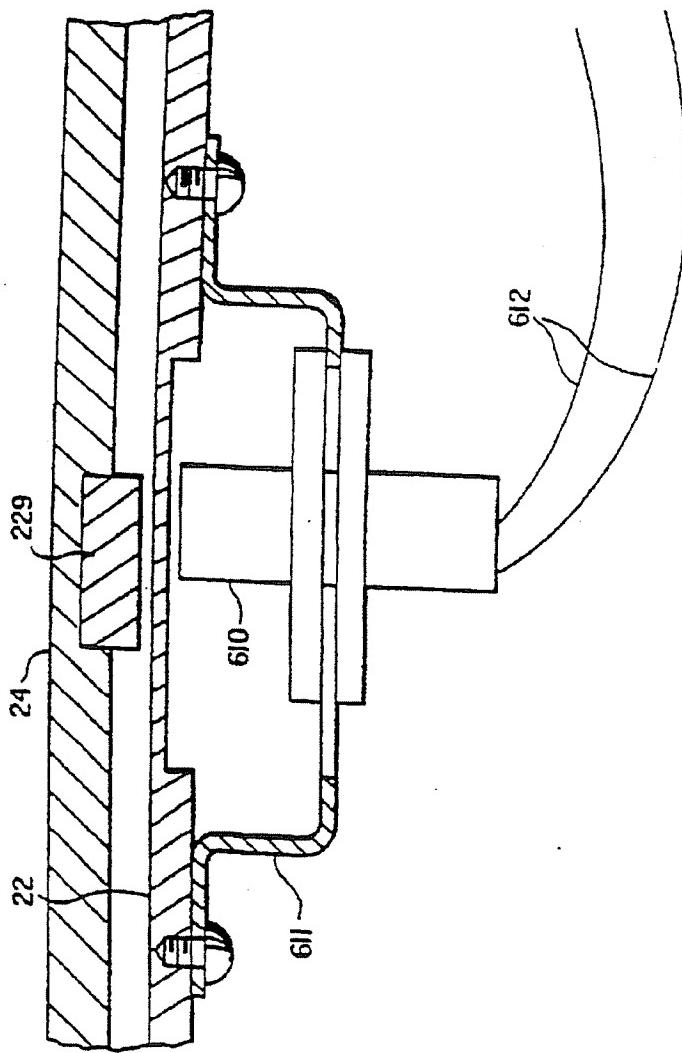
U.S. Patent

Dec. 7, 2004

Sheet 23 of 37

US 6,827,901 B2

FIG. 21



**U.S. Patent**

Dec. 7, 2004

Sheet 24 of 37

US 6,827,901 B2

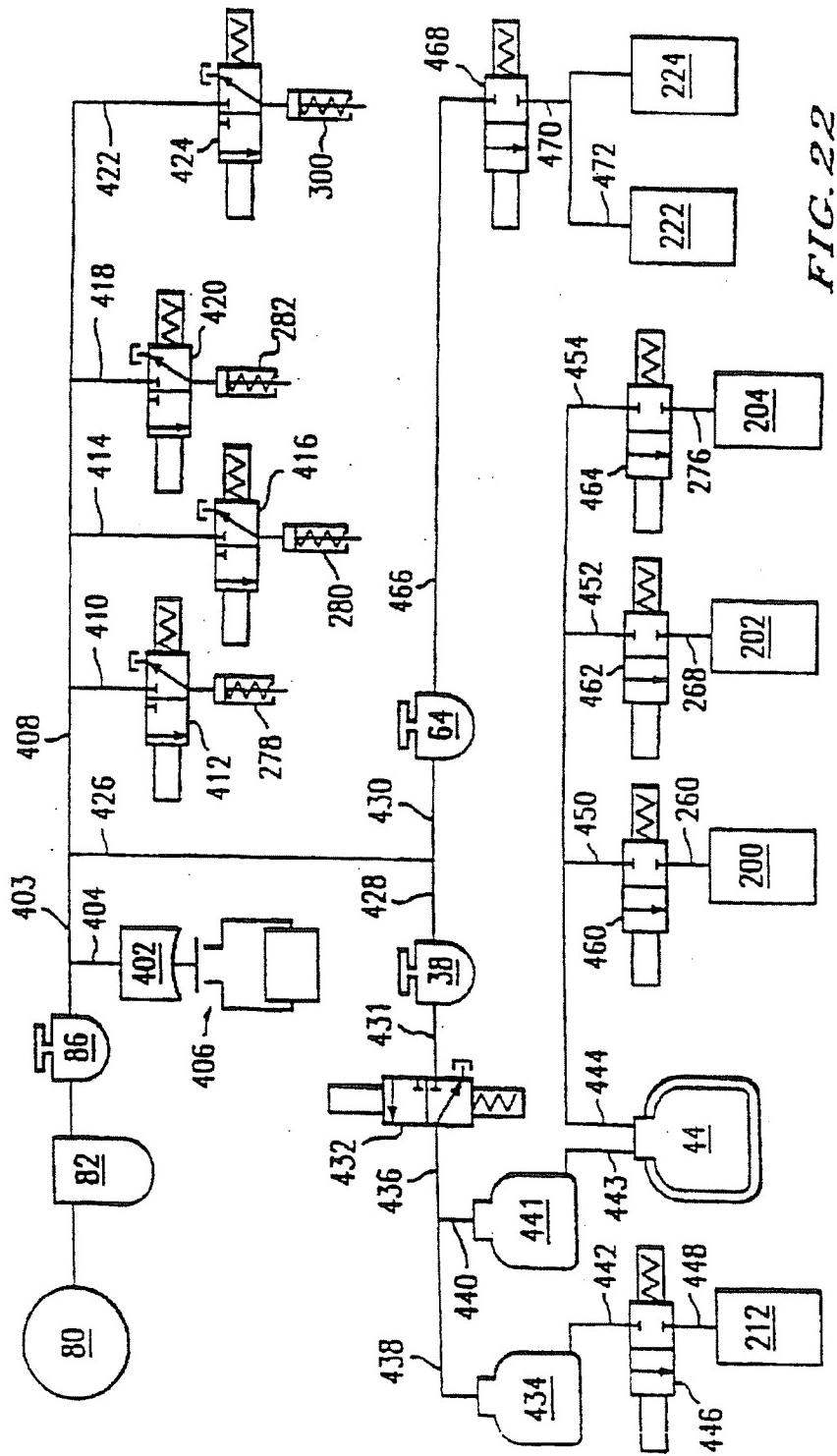


FIG. 22

U.S. Patent Dec. 7, 2004 Sheet 25 of 37 US 6,827,901 B2

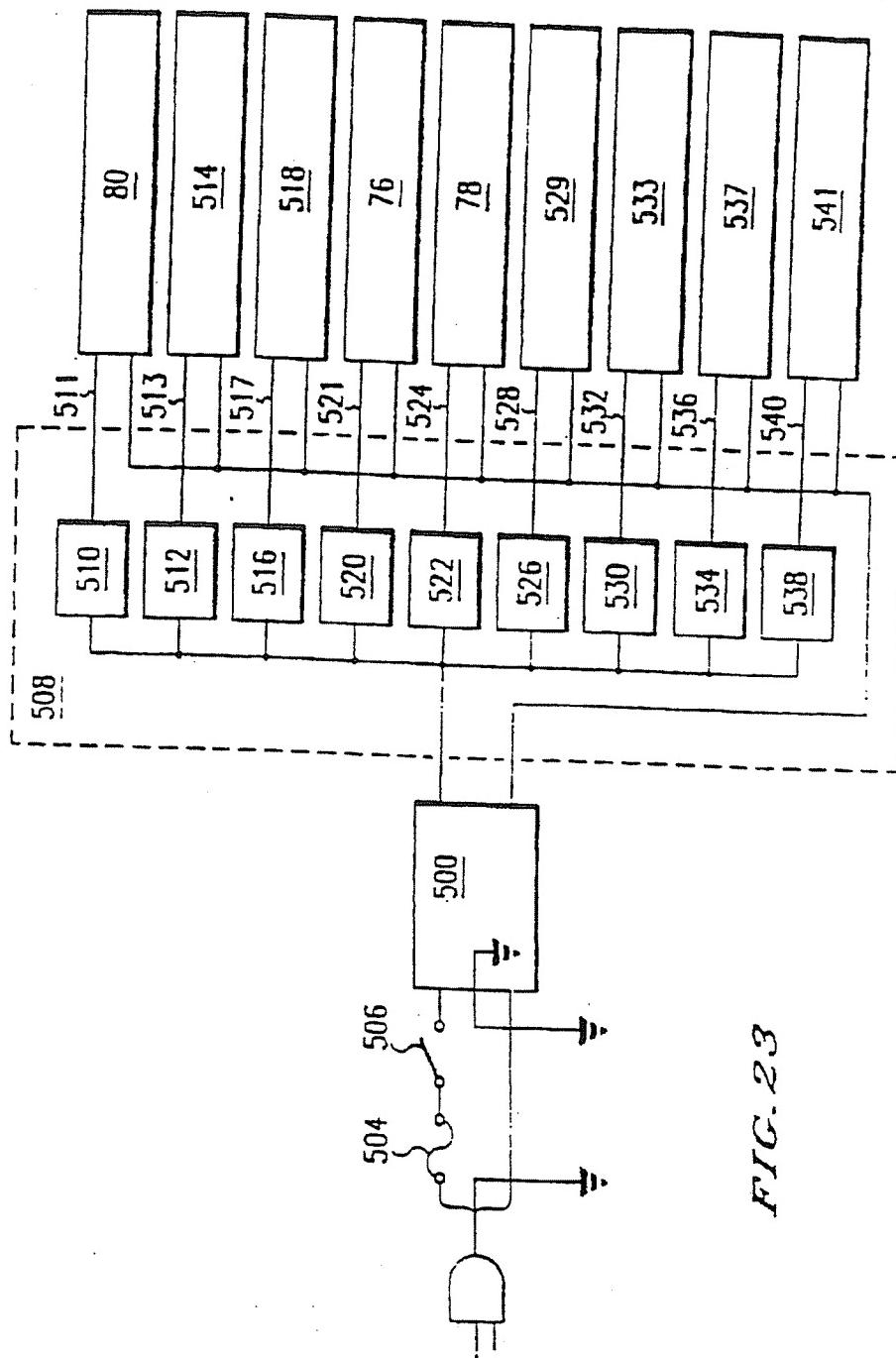
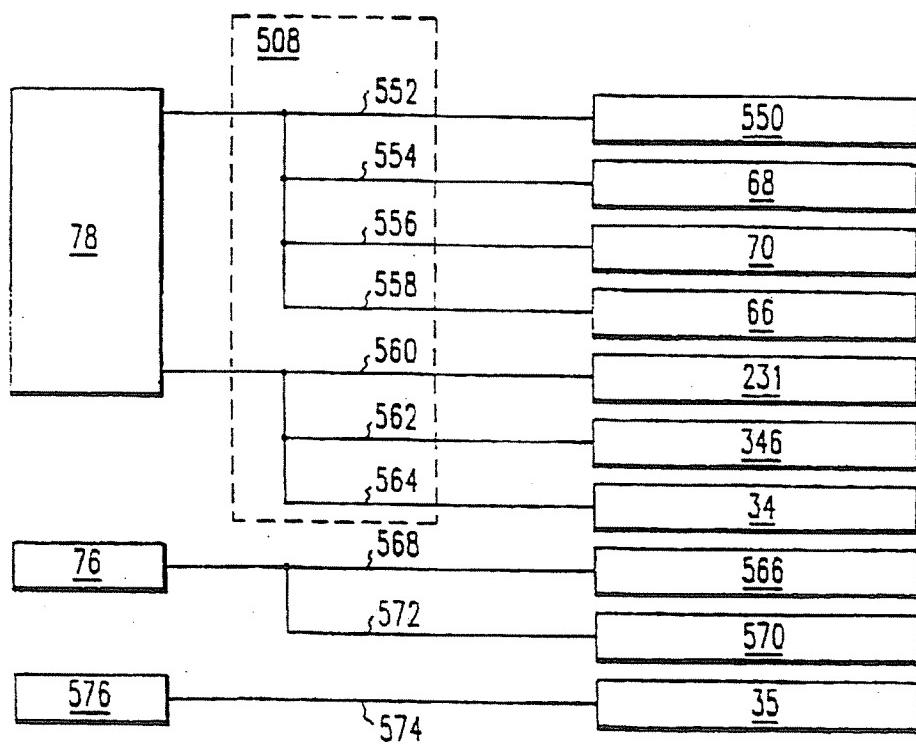


FIG. 23

U.S. Patent      Dec. 7, 2004      Sheet 26 of 37      US 6,827,901 B2



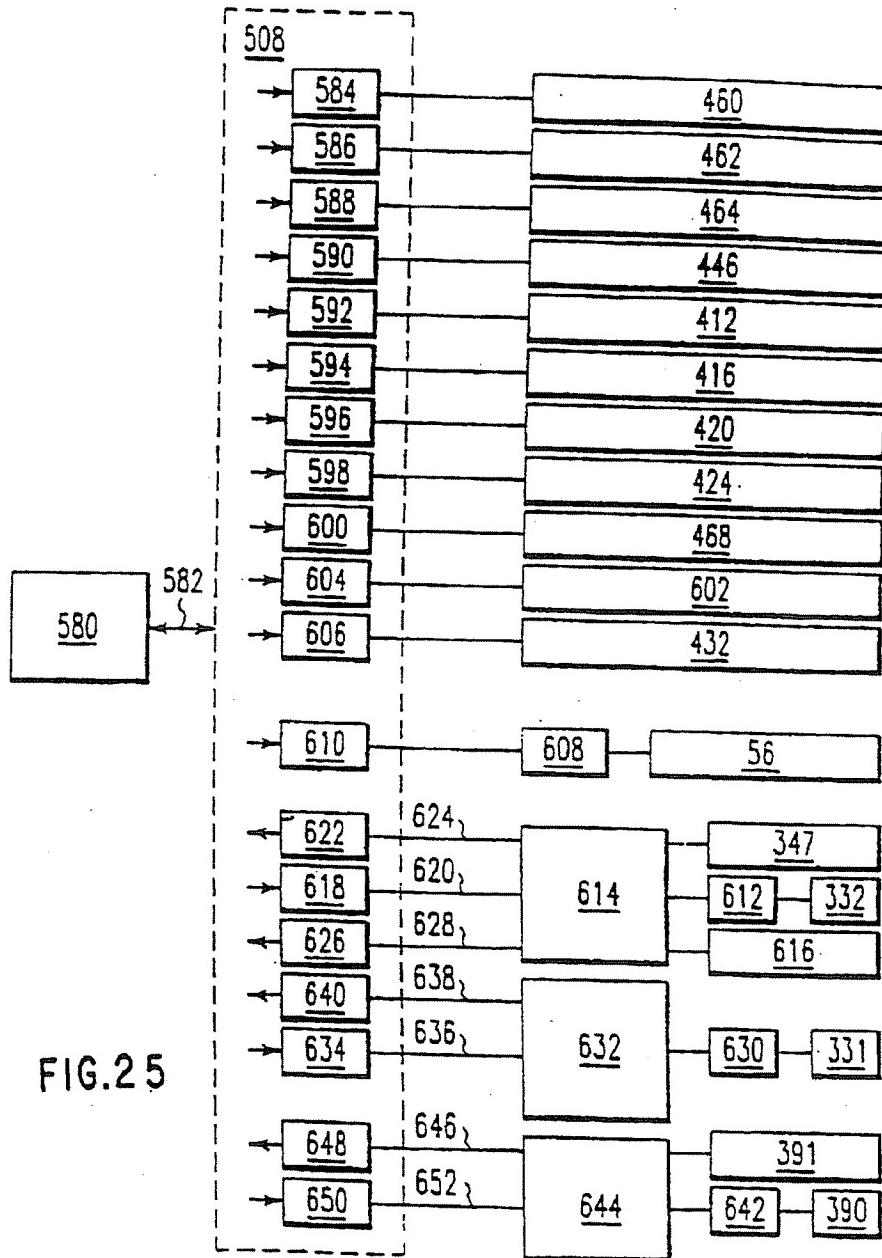
*FIG. 24*

U.S. Patent

Dec. 7, 2004

Sheet 27 of 37

US 6,827,901 B2



U.S. Patent

Dec. 7, 2004

Sheet 28 of 37

US 6,827,901 B2

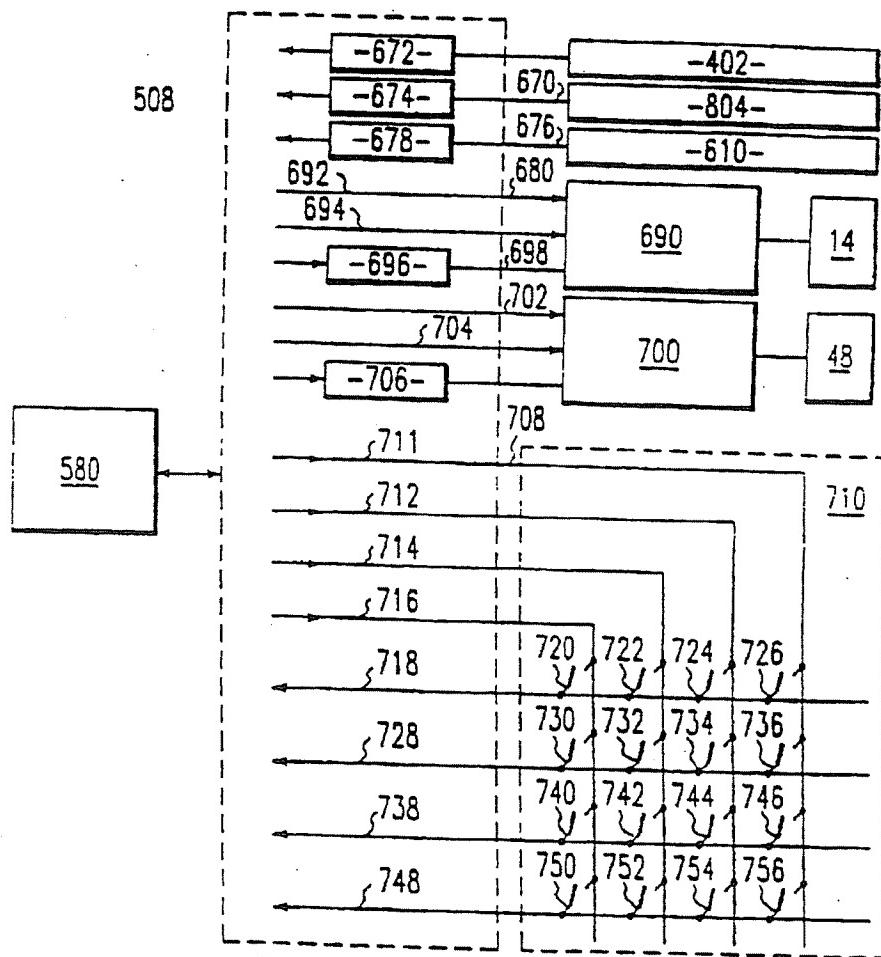


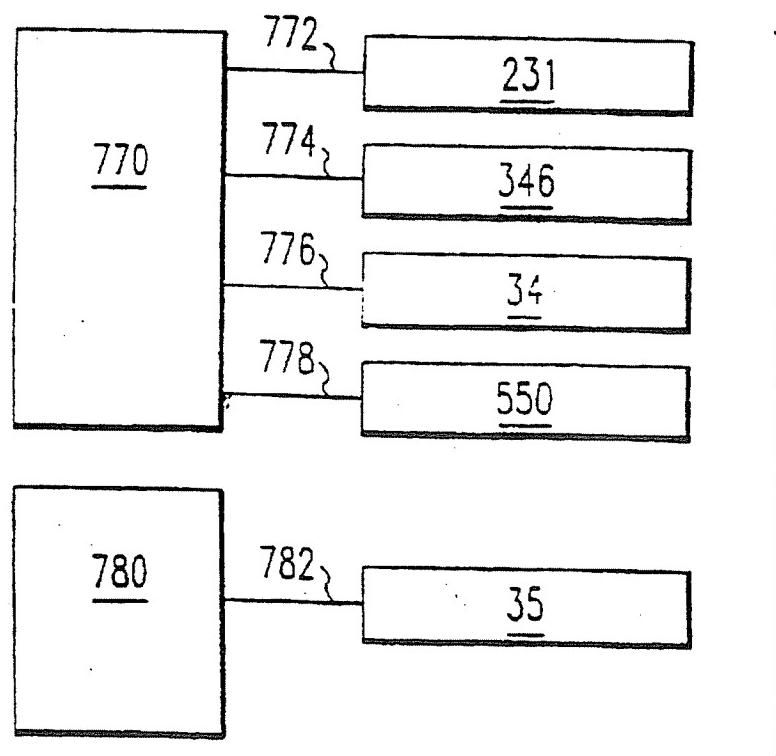
FIG. 26

U.S. Patent

Dec. 7, 2004

Sheet 29 of 37

US 6,827,901 B2



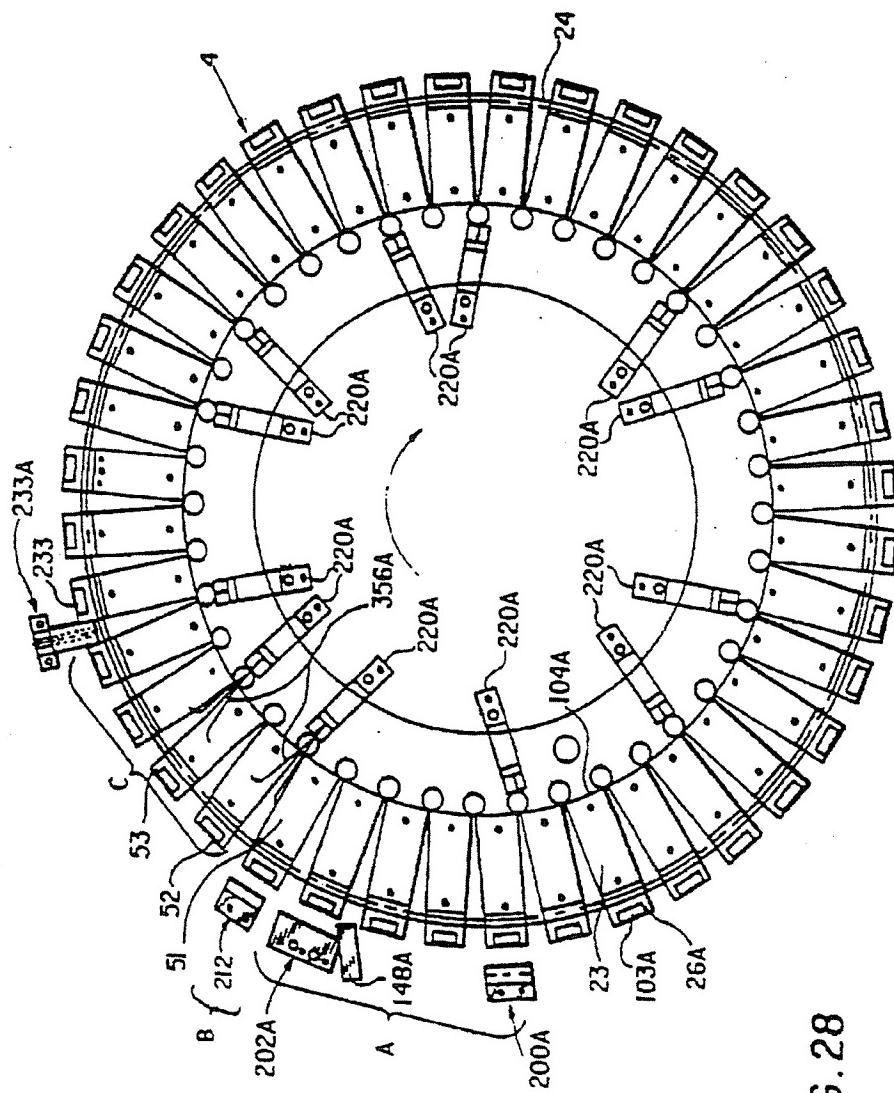
*FIG. 27*

U.S. Patent

Dec. 7, 2004

Sheet 30 of 37

US 6,827,901 B2



U.S. Patent

Dec. 7, 2004

Sheet 31 of 37

US 6,827,901 B2

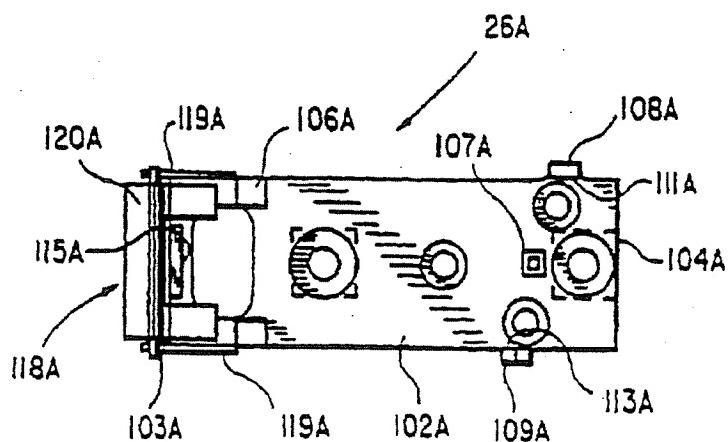


FIG. 29A

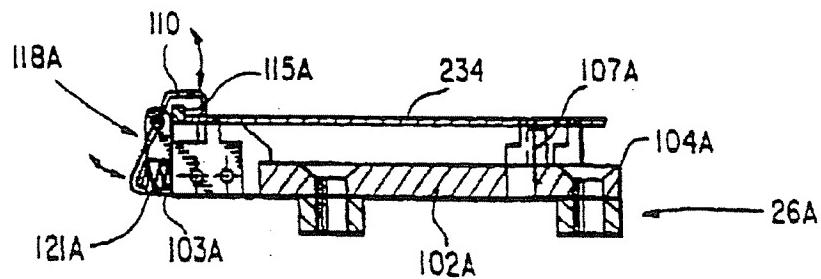


FIG. 29B

U.S. Patent

Dec. 7, 2004

Sheet 32 of 37

US 6,827,901 B2

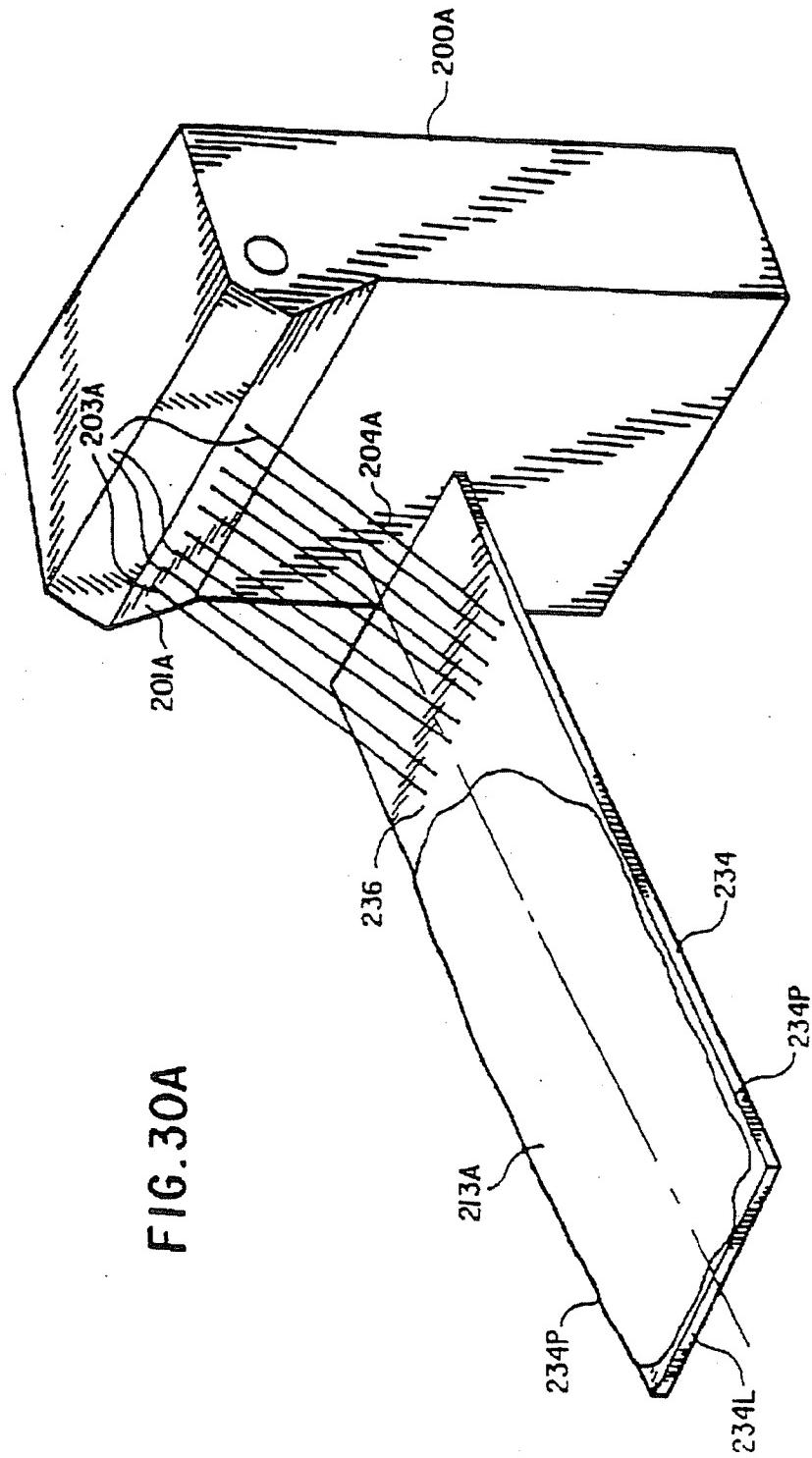


FIG. 30A

U.S. Patent

Dec. 7, 2004

Sheet 33 of 37

US 6,827,901 B2

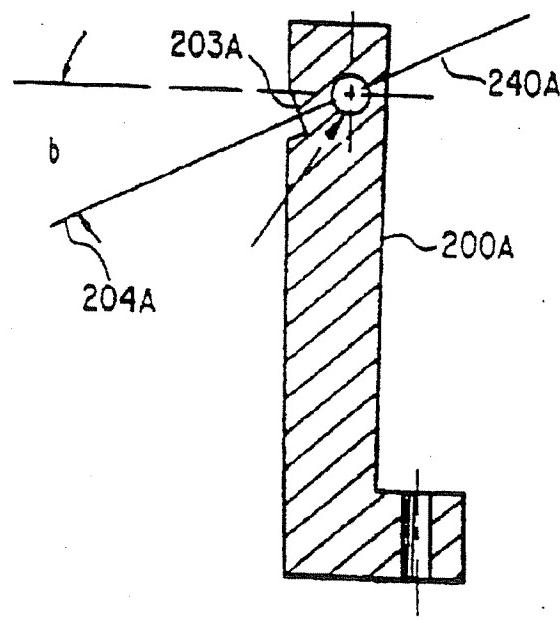


FIG. 30B